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ACUTE PSYCHOLOGIC DISTURBANCES IN THE COURSE OF HOSPITALIZATION OF PATIENTS WITH CHRONIC ILLNESS

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THE physician who has clinical responsibility for the care of patients suffering from chronic disease is well aware of the particular importance of psychologic factors in the medical management of such patients. The older clinical descriptions of these illnesses and their treatment frequently made mention of this fact. In recent years, under the heading of "Psychosomatic Medicine," there has been much emphasis and specialized research on the possibility of the precipitation or aggravation of physical symptoms and actual tissue alterations that might result from psychologic stress, past and present. This is an important task and still chiefly a matter for detailed research and elaboration of the special techniques appropriate to it. After an initial phase of overenthusiastic hopefulness about simple one-to-one psychophysiologic correlations, research in this area seems to be settling into a more sober attitude toward the task at hand. The ultimate goal in this task might be summarized as the elaboration of a physiology and pathophysiology of hope and despair.

Meanwhile, however, the clinician is faced with the present clinical responsibility for the care of patients with a variety of chronic illnesses. Episodes of acute psychologic distress are not infrequent during the hospital stay of the patient suffering from chronic illness. In this communication I would like to map out, through illustration, certain acute disturbances in behavior of patients suffering from chronic or relapsing illnesses during the course of hospitalization. Better understanding of the factors involved in such disturbances can lead to

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improved medical management of them and perhaps, at times, to their prevention. While the advice of a consulting psychiatrist in acute situations may be helpful and sometimes essential, he is of clinical assistance chiefly by understanding factors in the current situation of these patients that can be accessible to any physician whose attention is consistently directed to them in the course of his work as a clinician. The area to be illustrated might be summarized as an exposition of the means for systematic maintenance and expansion of the supportive and protective aspects of the doctor-patient relationship.

To emphasize the limited focus of this report, it would be well to sketch out briefly the broader perspective of psychologic disturbances during the hospital course of patients with chronic illnesses. The total psychologic response of any person to a stressful situation is the resultant of several factors. These are: (1) the nature and degree of the current stress, (2) the modes and range of psychologic response available to the patient as a result of past experience, and (3) the current environmental factors, including particularly supportive human relationships, that are available to the person in helping him to utilize effectively his means of coping with stress.*

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The focus of this paper is upon the last of these three aspects of the patient's psychologic response, that is, the current factors available to the person to help him effectively cope with stress. This is the variable of critical consequence in any attempt at treatment or prevention of psychologic responses that are handicaps to the patient and to the physician in his clinical job. Certain facts in the other two components of the patient's responses to stress need brief summarization, however, as they relate directly to the central issue of this report.

The degree of the current stress for the patient with chronic illness is often as great as any that may be found outside of the stress of overwhelming disasters or the stress of military combat. Indeed, certain patients live constantly on the edge of or in the middle of a "one person disaster." First are the facts of pain, disability, and threat to life itself. When these are not in the forefront, there is always the threat of exacerbation or recurrence. Dependence on drugs and on various limitations in activity for maintenance of states of relative health bring another set of problems. A sense of security and relief that goes with improvement is strongly qualified by a sense of conditionality, as, for example, "You will be all right *if* you take your insulin," or, "*If* you do what the doctor says, everything will go well." Even in states of relative health the patient has a sense of difference from others that fosters both withdrawal and resentment as alternatives to explaining constantly why one can't "go along with the crowd." In younger patients and in adolescents especially this conditionality of states of good health is a particular frustration and source of much chronic and bitter resentment. Being controlled and restricted by disease and by parental or other authority can easily become intermeshed. This is especially true if there has been much past experience with the unspoken or spoken formula, "If you are good, you will be rewarded."

*In terms of anxiety the same factors may be listed as (1) current anxiety-producing events and situations, (2) predisposition to anxiety, and (3) anxiety-reducing factors currently available including particularly significant human relationships.

Another major concern and source of anxiety for both patient and physician is uncertainty about prognosis. Remission and relapse is the rule rather than the exception. The physician cannot tell the patient when he will be better, if he will be better, or how much better or worse he can expect to be in what period of time. Both patient and physician may be buffeted by waves of optimism and hope only to have this changed to pessimism, if not despair. This denies the patient one of the greatest sources of assistance in the endurance of severe stress, namely, the reasonably certain prospect of future relief. For the physician these facts impose a special burden upon his task of maintaining within himself and of communicating to the patient a realistic expectation that things can get better and that the battle for health is not lost.

The current stresses, then, for the chronically ill patient are apt to be great in degree and duration. It is all the more important to remember how many people can make a reasonably good psychologic adjustment to great stress in order to understand the situations of those patients who do not. The latter group, we must assume, are in some way psychologically more vulnerable or more predisposed to experience anxiety. Of all the factors that predispose to anxiety the life experience of the patient is the most relevant and most accessible to useful understanding. Death, separation, and divorce of parents early in life are apt to be found in the life histories of patients who are unusually vulnerable. The infant and young child cannot cope with the stress of these losses by means of the adult mechanisms of grieving and reconciliation.[1] They use instead a variety of alternatives which leave them vulnerable to later situations that provoke feelings of loss or threaten to provoke such feelings.

Alternatively, a person may grow up in an atmosphere of unremitting strain or tension between parents who are never physically lost to the growing child but who seem continually at odds with each other and with the world. Another variety of experience that predisposes to unusual anxiety is less obvious. When a growing child feels that maintenance of any love and esteem from parents is entirely conditional to meeting a variety of expectations for "producing" and "inhibiting" he can come to feel that the business of living is like walking a tightrope—one step in the wrong direction and he plunges into an abyss of disapproval and abandonment. These experiences, indicated here in the briefest way, have a common resultant: fear of desertion by the people who count most. Whether the fear is of literal and physical desertion or of lack of love and approval, it results in difficulties later in life in trusting others. Chronic distrust is a particular problem when a person is under the necessity of trusting others with his health, with his body, or with life itself. In the course of chronic illness, particularly in the hospital situation, the patient is again put back into the situation of emotional and physical dependency, helplessness, and uncertainty that he has been trying to avoid, forget, and otherwise deny since the distressing experiences of his childhood days. In simplest terms, it is as if the need to be physically held and supported by someone brings with it a state of anxious concern that one will be suddenly dropped. This state of hypervigilance or hyperalertness to ominous developments in the environment is a critical issue in the patient's hospital experience. Its implications for understanding and

management of acute psychologic disturbances will be illustrated in the following anecdotal clinical illustrations.

CASE REPORTS

CASE 1.—A 37-year-old married woman was admitted to the medical ward service because of symptoms strongly suggestive of disease of the lower spinal cord. The clinical clerk, a senior medical student, spoke to the consulting psychiatrist about the patient's behavior. The patient was very apprehensive, unceasingly asked what her diagnosis was, constantly called various people to her bedside for one or another reason, and at times was tearful and unhappy. No reassurance seemed to help. In the course of discussion of the patient with the clinical clerk, the consulting psychiatrist suggested that the patient be asked what *she* thought her illness was. Two days later the clinical clerk reported that the patient finally had told him that she believed she had muscular dystrophy, and added that she had heard a lot about it on a recent television program. When told definitely that she did not have muscular dystrophy, there was a substantial reduction in her anxious behavior and tearfulness. She was later able to accept the need for an exploratory operation without undue anxiety, in spite of the clearly serious implications.

CASE 2.—A 52-year-old married man had had severe myasthenia gravis for several months. His disability, however, seemed out of proportion to objective measurements of strength and weakness. At home he had stayed fearfully in bed and, in fact, had been spoon-fed by his wife. During his first days on the hospital ward, for various administrative reasons, he had had to be moved from one room to another on two occasions. The consulting psychiatrist was asked to see the patient because of his excessive fearfulness and concern. In the course of several interviews the patient incidentally revealed that he felt the move from one room to another had been some sort of "preparation for death." The patient could explain this no further and it was only after he gained some confidence in the psychiatrist that he revealed this manifestation of his prior apprehension and dread.

CASE 3.—A 49-year-old woman with systemic lupus erythematosus became very ill and depressed during her third hospital admission. She needed special attention and care because of her critical condition. She was moved from a four-bed room into a single room opposite the nurses' station on the ward. At this point her depression deepened. Her negativistic behavior, including refusal of food, added immensely to the problems of caring for her. Much later she told the psychiatrist that she had seen patients moved into this room when they were dying and she felt that the move had sealed her fate.

CASE 4.—A 19-year-old girl in an acute episode of ulcerative colitis was in a single room on a medical ward. The psychiatrist was asked to see her because she refused to take medication, said that the doctors were trying to poison her, was sure she had cancer, and insisted that she had heard the doctors talking to her mother about burying her. This episode, which lasted only three days, had several interesting things about it. First, as the house staff noticed and as the patient herself said later, she had none of these fears when her mother was with her. Second, because of initial uncertainity about tuberculous enteritis, the doctors were wearing masks during the first days of her hospital stay. The patient said later she could not tell what they were thinking and felt that they looked grave which meant that her situation was grave. When she was on an eight-bed ward she said she could see that the doctors were equally serious about the other patients too, so she began to worry less about dying and about having cancer.[2]

CASE 5.—A 28-year-old man was in his sixth week of a complicated and prolonged convalescence from surgical correction of a patent interauricular septal defect when he became anxious, demanding, and bitterly complaining about injections. Only meperidine seemed to help his complaints of pain at the site of penicillin injections and also the pain in his chest. On one occasion he got out of bed, left the ward, and was found by the nurse in the waiting room, at which time he appeared dejected and talked vaguely of suicide. On another occasion in the middle of the night he demanded that the nurse call the doctor and when he felt that she was slow in doing so, he rushed to the telephone and tried to call the doctor himself.

The patient's convalescence from his operation had been uneventful until the second week when he began to have fever and some chest pain. As a result of these symptoms and of the en-

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suing diagnostic procedures, it was suspected that he might have subacute bacterial endocarditis, and accordingly treatment with penicillin had been started. A brief interview with the patient elicited the fact that he knew a good deal about subacute bacterial endocarditis, having had it once before. The patient was concerned about his long hospital stay, was fearful that his "subacute" was not responding to treatment, and supposed that the pessimistic facts were being kept from him by his physicians. The final straw in this latter suspicion was that on the day before his disturbed behavior began, not one, but three doctors had reassured him that things were going well. The patient interpreted this as an ominous sign on the basis of his own anxiety plus the fact that doctors, as he said, do withhold bad news from patients. There were many other things, some of them realistic and some of them distortions, which added up to the patient's conviction that he was not getting well. All this he had not spoken about to his physicians or to anyone else.

The psychiatrist listened and remarked that all this must be very distressing to the patient. At this point he cried a bit, spoke of his past distress, his high hopes for the operation, and his desperate anxiety and uncertainty to know whether the operation had been helpful. Two days later when the psychiatrist returned to the ward it appeared that the patient had suddenly changed for the better. The nurse said the he had been singing with his roommate and that he no longer complained about injections, required analgesics, and was demanding in his behavior with the nurses and doctors. At the second visit the patient indicated quite clearly that he had no wish for any further psychiatric interviews. It appeared that his confidence in his physicians had been re-established and the rest of his convalescence went smoothly, both medically and in terms of his behavior.

CASE 6.—A 32-year-old married man had been admitted to the medical ward suffering from myasthenia gravis. This patient had taken great pride in physical accomplishment and was by trade an expert mechanic. Myasthenia gravis represented a threat to his whole way of life and to his particular methods of dealing with anxiety. The psychiatrist was asked to see him because of recurrent panicky episodes on the ward which had also occurred during his life outside the hospital before admission. At home, during one such episode, he had rushed out of the house and had run until he collapsed. The patient described the awful feeling which sometimes came "out of the blue" at night. On one occasion he called the nurse to his room, told her to stand there, talk, and hold his hand. As he explained later, this helped him come out of his panicky reaction. After a while he said he heard what the nurse was actually saying, began to get interested in it, and between this and holding her hand was able to get himself out of this particular spell.

The type of support that may be helpful at such times is well indicated in what this patient asked for and got from the nurse. Physical contact and voice tones are extremely important in coping with reactions of panic.[3] Several days after the episodes of panic, a different problem arose. In the room next to the patient another patient suffering from the same illness, myasthenia gravis, died during the night. The question arose as to whether the patient should be told what had happened if he inquired, since it was felt that he was bound to notice the cessation of the noise made by the respirator. The psychiatrist advised that the patient be told the truth, because he believed that deception would be impossible and that not to admit the facts would confirm, to the patient, his distrustful anxiety. The patient did ask and was told the truth. He was upset about it but voiced his anxieties freely and there was no recurrence of his episodes of panic. He could manage the truly traumatic episode of his neighbor dying of the same illness as long as he felt that he had the support of his physicians.

CASE 7.—A 54-year-old married woman was admitted for study of sudden episodes of vomiting of four months' duration. Careful studies showed no organic basis for this difficulty. Moreover, the vomiting stopped after she came into the hospital. There was suggestive evidence that the attacks of vomiting might be triggered by intensely hostile feelings toward her husband. Once at 4 A.M., she had a sudden repetition of the vomiting. Careful questioning as to the events of this night revealed the following facts:

The patient had been awakened from a sound sleep by the loud cries and groans of a patient down the hall. She stayed awake listening to the other patient with mounting irritation and had the flickering thought, "It was better that the Lord take someone than that they suffer." She dozed off, then awoke again in the early morning to realize that the ward was silent. She had the sudden thought that the patient must have died, began to feel uneasy, and, in the course of a few

minutes, began to vomit. Thus an apparently unexplained episode of vomiting became more meaningful when the details of the night's events on the hospital ward were elicited. This episode provided additional evidence for the diagnostic suspicion that guilt over hostile feelings played a significant part in the genesis of the patient's symptom.

CASE 8.—A 46-year-old man, convalescing uneventfully in his second week from an acute myocardial infarction, had suddenly decided to leave the hospital and persisted in this intent in spite of forthright explanations by the medical house staff of the seriousness of his condition. The patient had given as reason for his signing out that there were urgent problems at home which needed his attention. The consulting psychiatrist was asked to see if he could persuade the patient to stay in the hospital. It developed that what particularly bothered the patient, as he put it, was "being spoon-fed by women." He had been on a program of "absolute bed rest." It was suggested to the medical staff that his medical regimen be liberalized, that the patient be allowed to feed himself and sit up a bit. This was done and the patient stayed in the hospital for the desired period of convalescence.

CASE 9.—The psychiatrist was called to see a 22-year-old single woman because of the possibility of "psychosis" or "feeblemindedness." The patient had been in the hospital a number of weeks. Initially suspected of having tuberculosis, it developed that she had a lung abscess which was eventually drained surgically. Recently she had been most uncooperative about postural drainage, had repeatedly smoked in bed (a fire hazard), had persisted in breaking her regimen of bed rest, and most recently had urinated in the waste basket on the ward. Now she was going to leave the hospital with disregard of any proper concern for her still serious medical condition. What the psychiatrist heard from the patient, after an initial period of sullen and negativistic silence, was that she still feared that she had tuberculosis from which an elder sister had died. She was in complete despair about ever getting better and felt that she might as well die at home. The patient, a high school graduate, was an intelligent and sensitive person. She was reacting, however, to the physicians and nurses with a pattern of behavior which had been developed in response to an overanxious and overprotective mother. A liberalization of the medical regimen and greater understanding on the part of the staff of the background of her behavior proved sufficient to the occasion. The patient did not leave the hospital, became more cooperative, and finished out her hospital stay without further significant behavior difficulties.

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DISCUSSION

Perceptions and Meanings of Hospital Experience.—Physicians understand but sometimes forget that what is commonplace to them in hospital experience may seem strange or threatening to a patient. Explanations of procedures, of a need for operation, or of a medical regimen are commonly given the patient so that he may understand and cooperate in the necessities. But it is difficult to keep in mind how widely different the world and values of the patient can be from the world and values of the physician. This difference is particularly true of the patient suffering from chronic illness at a time of acute exacerbation of symptoms.

Even more difficult to appreciate is the fact that perception, and the sensory impressions through which we orient ourselves to the outside world and to our bodily selves, may be altered, not only by disease and drugs, but by anxiety. We are familiar with the grosser distortions of perception in the form of symptoms in certain psychologic illnesses. In the hysteric patient we are acquainted with anesthesias, paresthesias, visual impairments (blindness and so-called "gun-barrel" vision), as well as pain. Auditory and visual hallucinations in some psychotic patients are other examples. Even here it is difficult to distinguish alterations in perception of events from alterations in the meaning and interpretation of events. Where the alterations are less dramatic and more transient,

distinction between perception and meaning is even more difficult to ascertain.[4-8] Psychologic research is again devoting much attention to this matter. Scientifically inexact as it may be, we will have to consider together the alterations of perception and of the meaning and interpretation of his perceptions to the patient.

In six of the nine examples cited (Patients 1, 4, 5, 6, 8, and 9) there were significant distortions by the patient of usual events of hospital routine and usual gestures and behavior of professional personnel. The problem of the first patient is of particular and recurrent importance in this age of organizations devoted to spreading knowledge and presumably understanding of special diseases. A situation of diagnostic uncertainty "confirmed" her suspicions of having muscular dystrophy. To her, diagnostic uncertainty meant that the doctors were withholding the bad news. In Patient 9 an initial diagnosis of tuberculosis was corrected in the minds of her physicians, but the fear-laden meaning, in terms of death and utter dependency on her mother, lingered on with the patient. In Patient 4 an inability to see the facial expression of her physicians and nurses because of masks "confirmed" the patient's fears of dying, of having cancer, or of being poisoned. In Patient 5 the too often repeated reassurance that he was recovering "confirmed" the patient's fear that he was not. Being moved from one room to another was "evidence" of being prepared for death to Patient 2.

It can be seen that descriptively these special meanings of events to the patient vary all the way from correct but dreadful understanding of events, through quite understandable misconceptions, to frank if temporary delusions of psychotic proportions. The important common factor in all of these reactions is that they render the patient more distrustful of his environment in a situation where he wishes and needs to be able to feel support and trust. Whether there is a correct perception with ominous significance, a correct perception with misinterpreted significance, or a major distortion of an event, the patient commonly keeps the perception and its meaning to himself because he feels that only further harm can result from speaking about it. The fear is that physicians and nurses will be irritated or will view his "childish" fears as ridiculous or "crazy." Alternatively, the patient fears that talking about matters will only confirm what he already suspects. It does not always happen so, but it is important to note that speaking about such matters to somebody is often sufficient to reduce the apprehension a considerable amount. When apprehension is reduced, some of the distortions of perception and meaning disappear very quickly, much as terrors that build up at night disappear during the daylight hours.

Distortions of perception and meaning are easier to understand as operational facts than to trace to their multiple origins. Relevant factors in the patient include social and cultural background, educational levels, past hospital experience and prior experience with physicians, unconscious determinants of character structure and neurotic disposition, as well as organic impairments of perception and of the integration of perceptions into patterns of meaning. Operationally, however, whatever the origins of the distortions, when anxiety mounts to a certain point there is a tendancy toward rigid all-or-none organization of the patient's perceptions into the channels of a dichotomy, "ominous vs. nonominous." This very organization of the patient's attention effectively precludes

experience that might be relaxing, pleasant, or reassuring. The final state preceding some acute psychologic disturbance might be characterized as one in which nothing but bad news can make an impression on the patient. Moodiness, silence, restlessness, and apprehension often characterize the outward manifestations of such situations.

The Presence of Rational and Irrational Fears.—For patients with chronic illness, distortions of perception and meaning of hospital events contribute to states of fear and apprehension which go unmentioned by the patient and which in turn foster feelings of anxious distrust (Patients 1, 2, 3, 4, 5, and 9). Patient 5, for example, started with a correct perception of a serious complication of his postoperative course. He kept his feelings of distress and his fears of never getting well to himself, however, and as these built up and became too great they asserted themselves in the form of anxious, depressed, and complaining behavior. This behavior made a difficult convalescence more difficult for the nurses and physicians and evoked annoyance and disapproval from the hospital personnel. A critical point was reached when the patient interpreted the behavior of his physicians, who wished to be reassuring, as something threatening. An essential point in the rather dramatic change in his behavior was the fact that the psychiatrist recognized his concern and despair and expressed an appreciation of his emotional state as understandable. In this particular instance, this happened to be just enough to restore to the patient his feeling of self-confidence, which then, in turn, reached out to the people in his environment. Thereupon he did not hesitate to let the psychiatrist know that he was no longer needed and proceeded in his convalescence without further significant emotional difficulty.

While this is a dramatic illustration and certainly not characteristic or typical, it is true that persistently "uncooperative" or "demanding" behavior in respect to a hospital regimen and to hospital personnel is often modifiable when the special meaning to the patient of certain aspects of the hospital situation and experience are appreciated by the people on whom the patient depends (Patients 1, 6, 8, and 9).

The first patient interpreted much of the uncertainty and diagnostic procedure as confirmatory of her self-diagnosis of muscular dystrophy. These in turn were equated with hopelessness and death. When asked, however, what she thought she might have, she was easily able to express her fears about her self-diagnosis, and this in turn permitted a definite and flat reassuring answer. Much of her anxiety thereupon subsided. In Patient 8 there was a particular anxiety about "being spoon-fed by a woman." This patient no doubt had a character structure that overemphasized the need to be "manly" and equated sickness, weakness, and dependency situations with "feminine."

In the clash, however, of particular facets of character structure with various aspects of hospital routine it is more practical to make some modifications of the hospital regimen to solve the problem than to insist, as it seems to the patient, that he alter his character structure. This requires understanding what facet of the hospital routine is "eating the patient." In Patient 9, an underlying and uncorrected dread of tuberculosis and death was the source of an acute aggravation of infantile and intensely negativistic behavior. The pattern or envelope

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of the patient's behavior was undoubtedly fixed by the patient's early life experience, especially with her mother. A "no nonsense" reaction on the part of the professional staff only provoked more negativism on the part of the patient. Understanding the patient's dread and despair with some relaxation of the strictness of the hospital regimen diminished the exacerbation of infantile demand and spiteful behavior.

The Clinician's Role in Management of Acute Psychologic Disturbance in Patients With Chronic Illness in the Hospital Setting.—In the discussion so far, emphasis has been placed on the value of correct understanding of the sick person's world of rational and irrational fears and the attendant hidden misinterpretations and misconceptions of hospital events and experience that may silently build up in the sick person. Giving the patient a chance to get these matters into words can promote or restore a feeling of understanding and trust in the patient. This in itself may be extremely helpful in acute psychologic disturbances. It may also lead to additional helpful measures, such as the manner of using special nurses, prolonged visits from relatives, moving the patient into the company of other patients, or modification of a medical regimen. In some cases it can lead to definite reassurances to the patient about diagnosis and prognosis. Striking and favorable changes in mood and behavior will sometimes ensue in the face of apparently severe degrees of psychologic disturbance. Subsidence of acute disturbance does not mean guarantee against recurrence. Moreover, a pre-existing serious psychiatric illness may make itself known under acute stress of physical illness. Operationally, however, the latter situation can best be defined by taking the measures mentioned above. Then, if the acutely disturbed behavior does not subside, more definitive measures, such as psychiatric hospitalization, may have to be considered.

"Getting the patient to talk" is, and probably ought to be, the special expertness of the psychiatrist. Taking time or not having time is often thought of as a special problem for the internist. In patients with chronic illness undergoing acute exacerbations sufficiently severe to warrant hospitalization, neither lack of expertness nor lack of time is the main factor in the physician's understanding or not understanding how the patient feels. Physicians who have clinical responsibility for these patients often do take a great deal of time with such patients. There is, however, one recurrent factor of major importance, although surely not the only one, that may prevent the clinician from hearing and understanding this sort of problem in this patient. This is the doctor's assumption that any or all anxiety, depressive feelings, despair, or uncooperative behavior are the patient's response to the threat of illness, pain, disability and the threat to life itself. The physician's sympathetic identification with the patient can at times mislead him as to what the psychologic disturbance is "all about". It is as if the healthy physician, momentarily identifying himself with his sometimes desperately ill patient, were saying, "Yes, I understand that you feel anxiety, despair, depression, hopelessness, because so would I or anyone if they were in your spot." This overlooks the patient's capacity to adjust to illness, and to feel hope, even in severe illness, if there are feelings of support and trust in relation to the significant people in the patient's life, particularly to the

physician. Paradoxically, it underestimates the unique importance at such times of the physician's own relationship with the patient.

Thus, the physician's identification with the chronically ill patient under acute stress may make him jump to a conclusion that psychologic distress is a natural consequence of severe and disabling illness. At times, this results in premature reassurance to the patient and blocks communication from the patient as to what his distress is all about. Premature reassurance can be felt by the patient as an invitation to keep quiet and may thus reduce the chance of the patient getting into words what really is troubling him.

SUMMARY

Comprehensive management of acute psychologic disturbances in patients suffering from various chronic illnesses in the hospital setting requires consideration of the current stress the patient is under, the patient's predisposition to anxiety as a result of past experience, and the psychologic resources currently available and supportive to the patient in meeting these stresses. Predisposition to anxiety is an important consideration in shaping the form and mode of expression of the patient's reaction to the pain, disability, and uncertainty which are inevitable in these illnesses. On the supportive side is the trust by the patient in his doctor and in other hospital personnel. The critical issue in acute psychologic disturbance of various sorts appears to lie in the fact that the more these patients are under the real necessity of trusting others with their prospects for health, their bodies, and their lives, the greater their anxiety about being deserted by the very people on whom they depend and need. Such situations of fundamental anxiety evoke a reaction of hypervigilance or hyperalertness to any sign or clue in the environment that the expected "desertion" is coming about or may come about. This is so, independent of the fact that members of the professional staff may have little awareness of these feelings. In such situations anxiety-laden misinterpretations of perception and meanings of events in the hospital environment occur. The general behavior and reactions of significant people, especially doctors and nurses, are scanned for anything felt as strange or irregular, and minor differences in attitude or expression are felt to have special import. Such fear-laden distortions or meanings that are special to the patient tend to go uncorrected because the very anxiety that provokes them also makes the patient feel that talking about his fears can only make matters worse. The exclusive devotion of the patient's attention only to ominous or nonominous signs in the environment makes it almost certain that little attention can be given to potentially reassuring perceptions and exchanges with people. If no factor of relief enters the situation, the patient feels, and comes to be, in fact, more and more isolated from the protective and supportive quality of the relationships with the hospital personnel and especially from his physician. He is then exposed to the stress of his own worst interpretations of his illness and the hospital situation and is simultaneously deprived of the expectation of understanding and support from others.

In such situations a wide variety of acute psychologic disturbances, either as symptoms or as behavior, may make themselves manifest. Disturbances of

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psychotic proportion, signing out of hospital, severe anxiety attacks, episodes of frank panic, as well as intensification of depressive trends may all occur. The critical factor in the prevention of such episodes or in their management when they do occur lies in the understanding of or failure to understand the patient's "build-up" of fear-laden distortions of meaning of the events and relationships in the hospital environment, especially within the doctor-patient relationship. For the patient, getting things into words with the physician and feeling understood is the best antidote for such distortions. The realization that childish and irrational fears are not repugnant to the physician and can be heard and accepted as such is also a great help. This is true whether the distortion is an easily understandable misconception or, in fact, an actual delusion.

The chief source of error in the clinician's handling of the psychologic aspects of such situations is neither a lack of expertness or interest nor a failure to spend time with the patient. It is more likely to be an assumption on the part of the clinician that under stresses so great any anxiety or any psychopathology is a natural consequence of the realistically great stresses of the illness. Having, so to speak, made a "diagnosis," the physician fails to make further inquiry and may attempt prematurely, and, to the patient, unrealistically, to offer support and reassurance. Because in these situations the physician does not, in fact, understand what is troubling the patient, the reassurance does no good and may even be felt by the patient as an indication that he should certainly not voice his real concern and fears. If there is relatively sudden appearance of anxiety or of other manifestations of acute psychologic disturbance in the course of hospitalization of patients with chronic illness, the safest and most useful assumption is that these are not reactions to the actual illness or real threat, as the physician sees it, but more likely a reaction to threat of the supportive aspects of the patient-physician relationship.

At times the expert help of a psychiatrist may be desirable or mandatory. But it is hoped that this discussion with clinical examples will, in many situations, assist the clinician to enhance and expand the supportive and protective aspects of the doctor-patient relationship.

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A STUDY OF HYPNOTIC DRUGS IN PATIENTS WITH CHRONIC DISEASES

Comparative Efficacy of Placebo; Methyprylon (Noludar); Meprobamate (Miltown, Equanil) Pentobarbital; Phenobarbital; Secobarbital

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THE efficient use of the many available sleep-inducing drugs would be simplified if the physician had reliable data on the comparative efficacy of such drugs. Because controlled studies in this field[1-4] are a relatively recent phenomenon, knowledge remains fragmentary about even such old and popular hypnotics as phenobarbital, pentobarbital, and secobarbital.

Access to a group of chronically ill patients permitted us to seek answers to the following questions: What is the nature of the sleep problems in such a group? Is such a population of use in the screening and evaluation of hypnotic drugs? What drugs are most satisfactory in providing a restful night's sleep for such patients?

In regard to the last question, it was thought important to compare the performance of the three older barbiturates mentioned above—perhaps the most frequently prescribed sedative drugs in this country—with two new drugs differing in chemical configuration.

POPULATION

The data to be described were collected primarily from 46 patients, studied for 11 nights each, so that every patient received (on one night or other) each of the medications to be described below. In addition, ten patients were studied for one or more (but less than 11) nights, and thus failed to receive all of the drugs. Some of the latter were eliminated from the study for medical reasons (such as cardiac infarct), while others considered the medications employed in the study, or the study itself, less desirable than their usual routine, and requested cessation of the new medications.

While this total sample represents all the patients who were available for study over a period of five months in two chronic disease hospitals (Montebello Hospital and Baltimore City Hospitals, Chronic Pavilion), it is only a fraction of the total population of these institutions, which averages about 375 patients. The house and nursing staffs designated 90 patients as suitable for study, i.e., patients who were not senile, were not suffering from cerebrovascular insults which made communication impossible, did not present other language barriers, and were not so ill from their primary disease, or from hepatic or renal insufficiency, as to be considered unsuitable for this investigation by the doctors responsible for their care. Of this group of 90 patients, 31 presented no sleep problems of any sort, and were not studied further. Fifty-nine of the group had difficulty falling asleep, staying asleep, or both, and were scheduled for study. All but five of these described themselves as requiring aid both in falling asleep, *and* in staying asleep. Ten of the 59 patients were not fully studied, for the reasons cited earlier, and three were not studied at all, either because of medical complications or because of refusal to participate in the study.

The 46 patients who successfully completed the series of eleven medications had an average age of 60 years, ranging from 39 to 91. Seventeen were 50 years of age or less, while 12 were 70 years or over. There were 32 males and 14 females. Fifteen of the patients had never received an hypnotic drug, to their knowledge. Seven had occasionally received drugs, but were unaware of their nature. Of the 24 patients who either knew what they were getting nightly, or on whom records were available to supply this information, the drugs and incidence of administration were as follows: phenobarbital, 9 patients; pentobarbital 6 patients; chloral hydrate, 6 patients; secobarbital, 2 patients; amobarbital, 1 patient. There was no necessary correlation between the prescribed drug, and the preference of the patient; some were pleased with their usual drug, many were dissatisfied. In most cases the patient had been put on a given drug on a certain occasion and the order was then not changed, regardless of the drug's performance.

METHODS

Forty-four patients were studied in an experimental design consisting of four Latin squares (11 × 11). Each patient was allocated at random to a position in the Latin square, which then automatically determined the order of administration of the eleven medications. Each medication was thus given first an equal number of times, second an equal number of times, etc. Two additional patients received the eleven drugs at random. The medications were as follows: placebo (lactose), pentobarbital sodium* 0.1 and 0.2 Gm., secobarbital sodium 0.1 and 0.2 Gm., phenobarbital 0.1 and 0.2 Gm., methyprylon (Noludar) 0.25 and 0.5 Gm., and meprobamate (Miltown, Equanil) 0.4 and 0.8 Gm. All drugs were given in capsules, made up so as to be indistinguishable in appearance. The drugs were always given at roughly the same time (bedtime) for any particular patient, although the time for retiring varied from 8:00 to 9:30 P.M. for individual

*Although pentobarbital and secobarbital were given as the sodium salts, they will be referred to throughout the paper as pentobarbital and secobarbital. Phenobarbital was administered as such, in keeping with common clinical usage.

patients. No other medication was prescribed in the event of failure to achieve success with the specified drug, but in four instances an additional hypnotic medication was ordered by the house staff. In these instances, any additional sleep obtained after these "extra" medications was discounted. Patients were studied on successive nights, except for week ends.

Patients were interviewed by the same technician on the morning after each experiment, and were asked the following questions: "How did you sleep last night?" "How long did it take you to fall asleep?" "How long did you stay asleep?" "Did you sleep better than usual, worse than usual, or the same as usual?" If better or worse, "In what way?" "How do you feel this morning?" In addition, any spontaneous comments were recorded, as were any pertinent objective observations by the nurses or technician (who, like the patients, were unaware of the nature of the medications used on any particular night). On 248 of the experimental nights (contributed by 23 of the patients), data were available from the nurses' records as to total amount of sleep during the night, and periods of obvious wakefulness on the part of the patients. In only eleven of these 248 instances was there gross disagreement between the report of the nurse and that of the patient.

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RESULTS

To provide a complete picture of the results, it will perhaps help to present the data in several different ways:

1. *Analysis of Variance on Latin Squares (44 Patients).*—For the 44 patients involved in the four Latin squares previously described, statistical analysis* revealed homogeneity of error variance (Bartlett's test) in the four squares, regardless of which function (induction, duration, or over-all performance) was being considered. Accordingly, error variance, treatment means, etc., for the four squares were pooled for the final analyses.

a. *Induction of sleep:* For the purpose of this analysis, some arbitrary definitions were set up. Thus, all patients who took three hours *or more* to fall asleep were counted as "180 minutes," in order to assign values to some individuals who claimed not to have fallen asleep at all on a particular night. Also, any patient describing his induction of sleep as "right away" or "immediately" was given a score of "two minutes." Any patient describing the induction of sleep as a range ("in 20 to 30 minutes," for example) was given the midpoint of this range as a score ("25 minutes," in this instance). The results are shown in Table I.

TABLE I. AVERAGE TIME REQUIRED TO FALL ASLEEP (IN MINUTES) (44 PATIENTS)

PLACEBO	PENTOBARBITAL		SECOBARBITAL		PHENOBARBITAL		METHYPRYLON		MEPROBAMATE	
	0.1 GM.	0.2 GM.	0.1 GM.	0.2 GM.	0.1 GM.	0.2 GM.	0.25 GM.	0.5 GM.	0.4 GM.	0.8 GM.
87	46	40	55	36	65	51	45	57	66	70

*Analysis has been performed in the usual fashion, as described by Cochran and Cox,[5] pp. 106-109

Statistical analysis indicated that significant ($p < 0.05$) differences from placebo were demonstrated for all drugs except the higher dose of Miltown. (The latter just missed significance by as close a margin as the smaller dose just reached significance.) In addition, both doses of pentobarbital, the higher dose of secobarbital, and the smaller dose of methyprylon were significantly better than 0.1 Gm. phenobarbital and both doses of meprobamate.

b. *Duration of sleep:* As in the case of induction of sleep, certain arbitrary decisions were made for the sake of analysis. The frequently voiced description "I slept off and on all night long" was recorded as zero hours of sleep. Any description which consisted of a range of hours ("six to seven hours all together") was counted as the mean of the range ("6.5 hours" in this instance). Total hours during the night were counted, whether continuous or interrupted, but hours spent in sleep after breakfast were not counted. The mean figures are shown in Table II.

TABLE II. AVERAGE NUMBER OF HOURS SLEEP DURING NIGHT (44 PATIENTS)

PLACEBO	PENTOBARBITAL		SECOBARBITAL		PHENOBARBITAL		METHYPRYLON		MEPROBAMATE	
	0.1 GM.	0.2 GM.	0.1 GM.	0.2 GM.	0.1 GM.	0.2 GM.	0.25 GM.	0.5 GM.	0.4 GM.	0.8 GM.
4.9	6.6	7.4	5.9	7.1	5.9	6.0	6.5	6.5	5.9	6.4

All medications were significantly better ($p < 0.05$) than the placebo in maintaining sleep. In addition, 0.2 Gm. pentobarbital was significantly better than every medication except 0.2 Gm. secobarbital and 0.1 Gm. pentobarbital, and, in the case of the latter drug, it just missed being significantly better at the 5 per cent probability level. The higher dose of secobarbital was significantly better than 0.1 Gm. secobarbital, both doses of phenobarbital, and 0.4 Gm. of meprobamate.

c. *Over-all rating:* On the basis of answers to the question "How did you sleep last night?" patients were given arbitrary scores of one to four. One was given for "very good," two for "pretty good" or "fairly good," three for "poor" or "not so good," and four for "very bad" or "terrible." The mean scores are given in Table III.

TABLE III. AVERAGE OVER-ALL PERFORMANCE SCORE (44 PATIENTS)

PLACEBO	PENTOBARBITAL		SECOBARBITAL		PHENOBARBITAL		METHYPRYLON		MEPROBAMATE	
	0.1 GM.	0.2 GM.	0.1 GM.	0.2 GM.	0.1 GM.	0.2 GM.	0.25 GM.	0.5 GM.	0.4 GM.	0.8 GM.
2.5	2.0	1.6	2.1	1.6	2.2	2.0	2.1	2.1	2.1	2.1

All drugs were significantly better ($p < 0.05$) then placebo except 0.1 Gm. phenobarbital, which just missed achieving significance. The higher doses of secobarbital and pentobarbital were significantly better than all other drugs.

d. *Efficiency of Latin square design:* Two variables which might conceivably be important in experiments of this type are: order of administration of drugs, and interpatient differences in response to drugs. Analysis of the importance of order of administration indicates that this factor was not significantly potent in these experiments, but the variation between patients was the greatest single source of variance—larger than the contribution of treatment differences. If one calculates* the increased efficiency of using each person as his own control, figures of 25 to 40 per cent (depending on which parameter one is studying—induction, duration, or over-all performance) are obtained. These figures are an index to the increased number of patient-nights which would have been required in the absence of this control.

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2. *Results Described in Other Terms.—*

a. *Induction of sleep:* Another way of describing the results for induction of sleep is to enumerate those individuals falling asleep within a given period of time. Thus, one might set up an arbitrary level of performance—say, 30 minutes or less—and then compare the various medications with this end point in mind. In Table IV are listed such data from the 46 patients who received all eleven medications.

TABLE IV. NUMBER OF PATIENTS FALLING ASLEEP WITHIN SPECIFIED PERIODS OF TIME (TOTAL—46 PATIENTS)

MEDICATIONS	15 MIN. OR LESS	30 MIN. OR LESS	1 HR. OR LESS	2 HR. OR LESS
Placebo	8	16	24	36
Pentobarbital				
0.1 Gm.	15	33	38	42
0.2 Gm.	16	33	40	43
Secobarbital				
0.1 Gm.	10	26	37	42
0.2 Gm.	22	37	39	45
Phenobarbital				
0.1 Gm.	6	21	31	42
0.2 Gm.	9	28	36	42
Methyprylon				
0.25 Gm.	15	30	38	43
0.5 Gm.	9	26	35	39
Meprobamate				
0.4 Gm.	13	26	31	38
0.8 Gm.	9	21	31	37

*As per Cochran and Cox,[5] p. 112.

It is obvious that the selection of the criterion of effectiveness is crucial in interpreting the "activity" of these agents. For example, if one demands sleep within 15 minutes, phenobarbital could be classified as essentially inert. On the other hand, the establishment of a low standard of performance (two hours or less, for example) puts the data in a range where the "batting average" of the placebo is so high that one is actually utilizing only 20 per cent or so of the population to provide useful data. Such a situation obviously renders the establishment of significant differences between drug and placebo extremely difficult. In some instances, of course, it is difficult to be misled as to a drug's efficacy. For example, 0.2 Gm. secobarbital performed well by any criterion, since it provided very rapid induction of sleep (15 minutes or less) for almost half of the patients, sleep within 30 minutes or less for 80 per cent of the patients, and sleep within two hours for all but one of the patients. Almost as impressive in performance were both doses of pentobarbital and 0.25 Gm. of methyprylon.

TABLE V. NUMBER OF PATIENTS SLEEPING SPECIFIED PERIODS OF TIME

(TOTAL—46 PATIENTS)

MEDICATIONS	5 HR. OR MORE	6 HR. OR MORE	7 HR. OR MORE	8 HR. OR MORE	9 HR. OR MORE
Placebo	27	25	22	15	3
Pentobarbital					
0.1 Gm.	35	32	30	22	8
0.2 Gm.	42	41	39	29	11
Secobarbital					
0.1 Gm.	32	31	29	18	5
0.2 Gm.	40	38	35	29	11
Phenobarbital					
0.1 Gm.	32	29	24	13	7
0.2 Gm.	35	32	26	19	6
Methyprylon					
0.25 Gm.	36	32	29	21	9
0.5 Gm.	38	35	28	21	10
Meprobamate					
0.4 Gm.	33	29	25	20	7
0.8 Gm.	38	33	29	21	8

b. *Duration of sleep:* One can likewise describe the results for duration of sleep by enumerating those patients sleeping for certain minimal periods of time. In Table V are presented such data from the 46 patients receiving all eleven medications.

Again one finds the higher doses of pentobarbital and secobarbital providing the outstanding performances. Pentobarbital, in 0.2 Gm. doses, provided 91 per cent of the patients with at least five hours of sleep, while secobarbital (in similar dosage) provided this effect in 87 per cent. Even if one picks seven hours of sleep as the criterion, 0.2 Gm. pentobarbital and secobarbital

performed satisfactorily for 85 per cent and 76 per cent, respectively. Of interest is the relatively poor performance of 0.1 Gm. phenobarbital, and the only slightly better results achieved by doubling this dose. There are suggestions that increasing the dose of all the drugs prolonged their effect, but the increments obtained with phenobarbital, methyprylon, and meprobamate were somewhat less marked than with pentobarbital and secobarbital.

In most instances, it was fairly evident from the patient's remarks whether sleep had been continuous or interrupted. If one compares the performances of the eleven medications on the basis of providing six or more hours of *uninterrupted* sleep, the figures shown in Table VI are obtained.

TABLE VI. NUMBER OF PATIENTS OUT OF TOTAL GROUP (46) SLEEPING SIX OR MORE UNINTERRUPTED HOURS

PLACEBO	PENTOBARBITAL		SECOBARBITAL		PHENOBARBITAL		METHYPRYLON		MEPROBAMATE	
	0.1 GM.	0.2 GM.	0.1 GM.	0.2 GM.	0.1 GM.	0.2 GM.	0.25 GM.	0.5 GM.	0.4 GM.	0.8 GM.
13	21	22	20	22	11	19	22	15	16	25

c. *Over-all performance:* In Table VII are listed the number of individuals (out of a total of 46 patients) responding in the four general categories previously described, to the question "How did you sleep last night?" Included in this table are two columns labeled "Satisfactory Sleep" and "Unsatisfactory Sleep," which represent the pooled figures for the "very good—good" and "poor–terrible" responses, respectively. Using this yardstick of efficacy, all the drugs are clustered together at a level somewhat better than that of the placebo, except for the higher doses of secobarbital and pentobarbital, which were outstanding in providing a high percentage of satisfactory nights, and a low percentage of unsatisfactory nights.

One of the questions asked routinely of the subjects in this experiment related to the quality of sleep when compared with a "usual night's sleep." Unfortunately, questions of this sort are subject to difficulties arising from a shifting standard. For example, a subject's "usual" is one thing at the start of the study, but may change radically halfway through the study if he has had five or six superlative (or miserable) nights in a row. At times it was obvious that such a phenomenon was occurring, and suitable questioning could insure that the technician and patient understood each other. At other times, success was probably not achieved in this respect. At any rate, the data are presented in Table VIII.

On a number of occasions, patients spontaneously commented on the previous night's sleep. Typical comments were: "I haven't slept that well in years," or "That's the drug I want when this test is over," or "That was *it* last night!" The number of times such comments were made for the various medications is depicted in Table IX.

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TABLE VII. DESCRIPTION OF NIGHT'S SLEEP BY PATIENTS (TOTAL—46 PATIENTS)

(Number of Patients)

MEDICATIONS	VERY GOOD "1"	GOOD "2"	SATISFACTORY SLEEP "1" + "2"	POOR "3"	TERRIBLE "4"	UNSATISFACTORY SLEEP "3" + "4"
Placebo	12	13	25	9	12	21
Pentobarbital						
0.1 Gm.	19	13	32	9	5	14
0.2 Gm.	22	20	42	3	1	4
Secobarbital						
0.1 Gm.	17	14	31	11	4	15
0.2 Gm.	27	11	38	6	2	8
Phenobarbital						
0.1 Gm.	15	14	29	10	7	17
0.2 Gm.	21	10	31	10	5	15
Methyprylon						
0.25 Gm.	19	15	34	5	7	12
0.5 Gm.	18	14	32	5	9	14
Meprobamate						
0.4 Gm.	19	11	30	10	6	16
0.8 Gm.	16	17	33	7	6	13

TABLE VIII. COMPARISONS OF SLEEP AFTER DRUG WITH "USUAL" NIGHT'S SLEEP (TOTAL—46 PATIENTS)

(Number of Patients)

MEDICATIONS	BETTER	SAME	WORSE
Placebo	18	7	21
Pentobarbital			
0.1 Gm.	21	11	14
0.2 Gm.	29	13	4
Secobarbital			
0.1 Gm.	19	11	16
0.2 Gm.	37	2	7
Phenobarbital			
0.1 Gm.	20	7	19
0.2 Gm.	29	4	13
Methyprylon			
0.25 Gm.	24	10	12
0.5 Gm.	23	9	14
Meprobamate			
0.4 Gm.	21	9	16
0.8 Gm.	21	11	14

TABLE IX. INCIDENCE OF SPONTANEOUS REPORTS OF EXTRAORDINARILY FINE NIGHT'S SLEEP (TOTAL—46 PATIENTS)

PLACEBO	PENTOBARBITAL		SECOBARBITAL		PHENOBARBITAL		METHYPRYLON		MEPROBAMATE	
	0.1 GM.	0.2 GM.	0.1 GM.	0.2 GM.	0.1 GM.	0.2 GM.	0.25 GM.	0.5 GM.	0.4 GM.	0.8 GM.
8	13	21	15	19	12	13	11	18	14	15

3. *Side Effects.*—The incidence of untoward effects was astonishingly low considering that each drug was given half of the time in doses twice as large as the recommended "average dose." The number of patients describing untoward side effects ranged from 4 to 10 for the various drugs and the placebo. When compared with the placebo in terms of *number* of patients reporting toxic effects, none of the drugs, in the doses employed, seems to have produced significantly higher toxicity. *Qualitatively*, however, the active drugs may have produced more reports which might be classified as "residual sedation," "hangover," etc. The data are as follows:

Placebo (seven patients): One dizzy; one headache; one headache plus dizziness; three gastrointestinal disturbances (one diarrhea, one heartburn and vomiting, one nausea and vomiting); one sleepy, with additional sleep after breakfast.

Pentobarbital, 0.1 Gm. (five patients): One "logey head, eyes blurry, nervous"; one sleepy; one "weak"; two gastrointestinal disturbances (one nausea, one "gas, constipated, dizzy").

Pentobarbital, 0.2 Gm. (ten patients): One headache and dizziness; one "heavy head" and grogginess; one additional sleep after breakfast; seven sleepy.

Secobarbital, 0.1 Gm. (five patients): One "logey head, nausea, vomiting"; two shaky and nervous; one drowsy; one "drunk and dopey."

Secobarbital, 0.2 Gm. (seven patients): Two dizzy; one additional sleep after breakfast; one sleepy; one "drunk and dopey"; two "groggy and dopey."

Phenobarbital, 0.1 Gm. (four patients): Two "sleepy and groggy"; one "drowsy all morning"; one additional sleep after breakfast.

Phenobarbital, 0.2 Gm. (five patients): Four sleepy; one "dopey."

Methyprylon, 0.25 Gm. (six patients): One headache; one "dopey and sleepy"; three sleepy; one "crazy feeling."

Methyprylon, 0.5 Gm. (ten patients): Two headache; two dizzy; one sleepy and headache; one drowsy; two additional sleep after breakfast; one "short of breath"; one "sweaty, short of breath, headache."

Meprobamate, 0.4 Gm. (seven patients): Three additional sleep after breakfast; one drowsy; one "dopey" and additional sleep after breakfast; one "weak and tired"; one frequency of urination.

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Meprobamate, 0.8 Gm. (eight patients): Three "dopey and groggy"; one "headache, groggy, heat sweats"; one "headache, eyes blurry, palpitation"; one headache; one additional sleep after breakfast; one "heavy head, restless, vomited."

It should perhaps be pointed out that the resumption of sleep after breakfast, occasionally reported by the patients, was usually not considered unpleasant by them, and is listed for completeness rather than as a particularly annoying "side effect."

Another point which may be significant is that in the case of all five drugs, the higher dose was associated with a slightly higher incidence of side effects.

4. *Results on Incompletely Studied Patients.*—The data on the ten patients incompletely studied are not presented because of the paucity of information contained and the belief that to pool such data with the other data would not serve much purpose. Suffice it to say that such trends as are suggested in these data are in keeping with the results previously described for the 46 completely studied patients.

DISCUSSION

An attempt may now be made to answer the questions posed in the introduction. If the population sample examined in this study is representative of chronically ill people, it would appear that sleep difficulties constitute a real problem for such patients. This is not surprising, in view of their restricted activity, afternoon "cat naps," and the general boredom of many with their surroundings. We found our population not only suited to studies of this type, but actually eager (for the most part) to cooperate in such studies. Their desire for a medication which will solve their sleep problems, plus their enthusiasm for a change in their everyday routine, and an opportunity for social contact with a friendly, outgoing technician, probably all contributed importantly to the relative ease with which this study could be completed.

There were some difficulties, nevertheless. A few patients were unwilling to be "guinea pigs." Some others were frightened off by the discouraging remarks of two patients who started the study and then stopped because of "poor results." The eagerness of the patients who did participate may explain in part the surprisingly high placebo rate in this group, most of whom claimed that they "would not sleep a wink" without some hypnotic drug, and frequently commented on their poor sleep during the week ends which interrupted the sequence of experimental days.

The results show that the total population employed could, however, distinguish between inactive and active medications. The two new drugs studied, methyprylon and meprobamate, seem to possess definite hypnotic activity. The former, in a dose of 0.25 Gm., produced results essentially indistinguishable from those of 0.1 Gm. pentobarbital or 0.1 Gm. secobarbital. This dose (0.25 Gm.) is slightly higher than that (0.2 Gm.) marketed by the manufacturers of methyprylon, but it is doubtful if this difference in dosage would be important. Side effects were not excessive, and methyprylon would seem to be a new drug of considerable usefulness. Previously published studies[4,6] have arrived at similar conclusions. The higher dose of methyprylon did not seem to provide

any advantage over the smaller dose, which is in contrast to the case with pentobarbital, where 0.2 Gm. seemed considerably better than 0.1 Gm. in certain respects.

Meprobamate, a drug with interesting pharmacologic properties,[7-9] seems most comparable with phenobarbital, in the doses of each studied. The failure to produce sleep as rapidly as some of the other drugs is in keeping with previous studies[7] in animals, which indicate that even intravenous injection of meprobamate is followed by a considerable lag period before definite objective effects are manifest. The observed prolonged effect of the drug is also in keeping with these previous studies.

The results with the three barbiturates are of considerable interest. Despite the almost complete absence of clinical data bearing on this point, pentobarbital, secobarbital, and phenobarbital are usually classed as widely different in performance. Our data do not bear out some of these postulated differences. For example, secobarbital in 0.2 Gm. doses can hardly be called an hypnotic of brief duration. Indeed, secobarbital and pentobarbital, in 0.1 Gm. doses, were at least as effective in providing maintained sleep as phenobarbital in this dose, and the latter drug was inferior to the former two when the doses of all were doubled. Nor can the results be attributed merely to delayed onset of action with phenobarbital, since the incidence of "hangover" with this drug was no greater than with the other two.

Secobarbital and pentobarbital also seem less different from each other than certain "clinical impressions" would suggest. In equal doses, the results we obtained with these two drugs are difficult to distinguish, whether one is considering onset of effect, duration of effect, patient's preference, or side effects. Both drugs performed well, and seem to provide considerable flexibility to the prescribing physician with shifts in dosage. It is suggested that one or both of these should serve as standards against which to compare new drugs.*

A few final remarks are in order concerning generalizations to other clinical situations from the particular one employed in the present study. It is perfectly possible that quantitative, and even qualitative, differences in effectiveness and toxicity of drugs would be observed if one were to examine these drugs in a group of acutely ill patients in the hospital, or in a nonhospital setting. Current studies in this department are testing this possibility. However, it is of interest that the data available at present give hope for believing that *comparative* performance of hypnotics in widely different situations is relatively consistent. For example, a comparison of trichloroethanol, chloral hydrate, and a placebo by three different groups[2] employing different populations resulted in essentially similar conclusions by the different investigators. The low incidence of toxicity with pentobarbital (even in 0.2 Gm. doses) in the present study compares closely with that reported in a previous study[1] of preoperative patients. The essential similarity in performance of pentobarbital and secobarbital has been

*It is difficult to avoid concluding that 0.2 Gm. secobarbital and 0.2 Gm. pentobarbital were outstanding in the present study, however one examines the results. Even if one performs statistical analysis of the data by the more rigorous manner (employing "ranges") suggested of late by certain statisticians, the higher doses of these two barbiturates are unequivocally effective, in contrast to the other medications.

previously reported by Goldstein[10] in experiments with medical students. All these findings suggest that suitably conducted trials of hypnotic drugs on *any* population may be considerably more reliable, for purposes of generalization, than clinical impression based on uncontrolled observations.

SUMMARY

1. A controlled clinical comparison has been made of placebo, pentobarbital, secobarbital, phenobarbital, methyprylon (Noludar), and meprobamate (Miltown Equanil), in 46 chronically ill patients.

2. The effects of two dose levels of each drug on induction and duration of sleep, and over-all performance, as described by the patients, have been described and analyzed.

3. Methyprylon (Noludar) and meprobamate (Miltown Equanil) have hypnotic properties, the former resembling pentobarbital and secobarbital, and the latter resembling phenobarbital, in performance.

4. The most satisfactory therapeutic results were achieved with 0.2 Gm. of secobarbital and of pentobarbital; these drugs are recommended as standards against which new drugs should be compared.

5. Unpleasant side effects were infrequent with all medications.

6. Chronically ill patients with insomnia provide a useful population for the evaluation of hypnotic drugs.

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ON THE MEASUREMENT OF PREVALENCE OF ARTHRITIS AND RHEUMATISM FROM INTERVIEW DATA*

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ARTHRITIS and rheumatism, either together or separately, have been included as items on a check list that was read to and/or handed to a respondent in at least thirteen household morbidity surveys[1] in the United States during the last twenty-five years. Tabulations from these surveys have been the principal source of national estimates of prevalence of arthritis and rheumatism. Although the exact phrasing of the questions in these surveys has varied, they have taken the general form, "Does anyone in this household have arthritis or rheumatism?"

It is the purpose of this paper to examine the relationship between responses to a question of this type on recently completed interview surveys in Pittsburgh and an independent classification of the same group of persons based on findings of a medical examination. To the best of our knowledge this is the first time such an investigation has been reported. The implications of these comparisons for the continued use of this question on morbidity survey questionnaires will be examined. While the comparisons relate directly only to the question of arthritis and rheumatism, the findings have broader implications for any estimates of prevalence prepared from survey data obtained by the interview method.

METHODS

A probability sample of households in the Arsenal Health District of Pittsburgh was drawn and interviewed in 1951. The general purposes of this sample have been discussed by Ciocco,[2] and its structure has been reported by Horvitz.[3]

The same household sample was again interviewed in June and July, 1952. The first of many health questions asked at this time related to arthritis and rheumatism. Of the 7,132 persons included in the 1952 household sample, 1,323 were selected for individual interviews during 1953-1954. These interviews were directed specifically at the single subject, arthritis and rheumatism. Later, 707 persons, a subsample of those interviewed individually, were invited

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to the health center for a medical history, examination, and x-ray studies. Some of the diagnostic difficulties encountered in examining people with mild and minimal manifestations of arthritis have already been reported.[4] This phase of the work was completed in September, 1954.

Seven hundred and seven persons had an opportunity to go through all three phases of the study. Of these, 429 (61 per cent) were examined, 195 (27 per cent) refused examination, and the remaining 12 per cent were unavailable for examination by reason of death, removal from the county, inability to locate, or refusal of the interview. This low completion rate presents a difficulty in making population estimates. Fortunately, from data on the three preceding interview surveys, detailed comparison can be made of those who were examined with those who refused. Only minor differences were found in examination rate by age, sex, income group, history of arthritis, joint pain, or joint swelling and many other variables. These differences, however, are insufficient to affect the conclusions to be presented here. Further discussion of this problem will be presented elsewhere.[5]

At each of the three stages of this study, a question specifically naming arthritis and rheumatism was used. In the 1952 household survey, the responsible individual at home was asked, "Does any member of this household have rheumatism or arthritis or other ailment of that type?" The interviewers for this study were mostly second and third year medical students who had a brief training period before going into the field. In the individual interview, the specified person was asked, "Have you ever had arthritis or rheumatism?" The inquiry here was made almost entirely by nonmedical interviewers with considerable previous experience in morbidity survey work. On the occasion of the clinic visit, the physician's first question, after the usual amenities, was, "Have you ever had any arthritis or rheumatism?" After that, the three physicians were free to follow their own preferred procedure for taking a medical history and doing a physical examination, though their reports were written on a standard form. On the basis of this examination, the physician recorded a diagnosis and the certainty with which that diagnosis was made.

From these diagnoses and certainty statements, the following subdivisions of the gradient of arthritis were established:

1. *Classical Arthritis.*—The physician reports that he is certain of the the diagnosis he has made, i.e., the case would fit a textbook description of one of the rheumatic diseases. Most of the persons falling into this category have degenerative joint disease, rheumatic heart disease with a history of arthritis, or other rheumatic conditions.* There were relatively few cases of classical rheumatoid arthritis.

2. *Definite Arthritis.*—The physician reports that he is certain that the individual has or has had some form of arthritis, but the differential diagnosis is not perfectly clear.

3. *Rheumatic Complaints.*—The physician reports that the symptoms and signs presented are those found among persons with joint disease but are not sufficiently distinctive to give the physician any confidence in his diagnosis.

*The conditions considered rheumatic are those listed in the Primer on the Rheumatic Diseases.[6]

4. *Questionable Complaints.*—This group is composed of persons whom the physician was unwilling to classify in one of the groups above and yet was not certain had never had any arthritis. Some people fall into this group because of communication difficulties; either inadequate command of the English language or inadequate education, or both. Obviously persons without physical signs of disease can be classified only on the basis of history.

5. *No Suspicion of Arthritis.*—Persons thus designated were felt to have been essentially free of rheumatic complaints throughout life. This classification was quite rigorous and was not used unless the physician was satisfied that he had taken an adequate history.

It is evident that other physicians might distribute the persons rather differently among the five categories described above. The fact that three physicians, with differing clinical backgrounds, participated in the work lends some additional reliability to the results, for the exchange of views on diagnosis was most helpful. Although relatively few changes were made, obvious errors were corrected and areas of disagreement were found and brought up for discussion. Presumably, the best agreement is at the two ends of the scale. Particularly, it seems unlikely that many of the persons classified as having no evidence of arthritis would be differently classified by other physicians.

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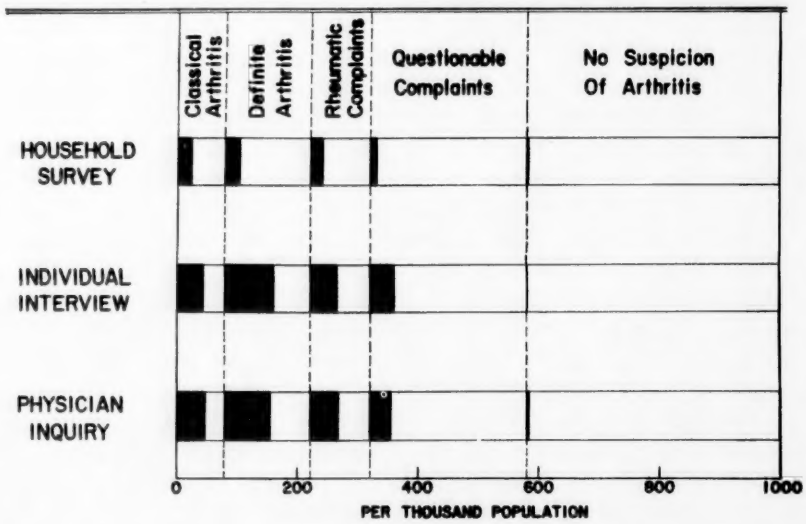

Fig. 1.—The relationship between positive responses to inquiry about arthritis and rheumatism in various interview situations; shaded areas, and clinical classification of the same individuals. Persons 15 years of age and older in the Arsenal Health District of Pittsburgh, 1952 to 1954.

FINDINGS

In Table I and Fig. 1 a summary is presented of the relationship between the answers to the questions obtained in the three different interview situations and the gradient of disease established at the clinical examination. The first points of interest are found in the marginal totals. It is apparent that arthritis

TABLE I. THE DISTRIBUTION OF PERSONS BY GRADIENT OF ARTHRITIS AND CLASSIFICATION ON CERTAIN QUESTIONS ABOUT ARTHRITIS AND RHEUMATISM, LIFETIME PREVALENCE RATES PER 1,000 PERSONS 15 YEARS OF AGE AND OVER FOR THE ARSENAL HEALTH DISTRICT OF PITTSBURGH 1952 TO 1954

PHYSICIAN CLASSIFICATION	HOUSEHOLD SURVEY REPORT OF ARTHRITIS OR RHEUMATISM		INDIVIDUAL INTERVIEW REPORT OF ARTHRITIS OR RHEUMATISM		REPLY TO PHYSICIAN INQUIRY REGARDING ARTHRITIS OR RHEUMATISM			TOTAL
	YES	NO*	YES	NO*	YES	DON'T KNOW	NO	
Classical Arthritis	21 (40)	50 (15)	42 (43)	29 (12)	47 (41)	13 (11)	11 (3)	71 (55)
Definite Arthritis	24 (47)	123 (47)	82 (51)	65 (43)	77 (50)	47 (30)	23 (14)	147 (94)
Rheumatic Complaints	19 (38)	82 (32)	44 (40)	57 (30)	47 (37)	36 (22)	18 (11)	101 (70)
Questionable Complaints	9 (18)	253 (92)	40 (25)	222 (85)	35 (21)	56 (31)	171 (58)	262 (110)
No Suspicion of Arthritis	2 (3)	417 (97)	1 (2)	418 (98)	4 (2)	12 (5)	403 (93)	419 (100)
Total Responses	75 (146)	925 (283)	209 (161)	791 (268)	210 (151)	164 (99)	626 (179)	1000 (429)

*"Don't know" answers, amounting to about 1 per cent of the total, have been included here.
( ) Contain the numbers of persons from which the estimates are made. It should be remembered that the numbers do not convert directly into percentages because the sampling rates differ in various strata of the sample. For the computational methods employed, see Cochran,[7] Section 5.3.

is found more commonly than previous estimates from this country would suggest. These estimates for persons 15 years of age and older, in the Arsenal Health District of Pittsburgh, give values for classical arthritis at 71 per 1,000, and classical plus definite arthritis at 71 plus 147, or 218 per 1,000. It is interesting to observe the relationship between household survey "yes" answers, 75/1,000, and classical arthritis, 71/1,000. Furthermore, a similar relationship exists between the rate for positive responses on the individual interview, 209 per 1,000, and the rate for classical plus definite arthritis, 218 per 1,000.

On entering the body of the table, it is seen, however, that the correspondence of these rates is fortuitous. For example, the number of persons per 1,000 who were found by the examining physician to have classical arthritis and for whom a positive response was given to the household question is only 21, or less than one-third of the respective marginal totals. Moving on to the individual interview, the situation is somewhat better, for here 42 plus 82, or 124 persons per 1,000 have either classical or definite arthritis and respond positively to the question. This is something over one-half of the respective marginal totals, 209 and 71 plus 147, or 218. It further appears that positive answers are found in considerable numbers among those with questionable complaints, and occasionally among those with absolutely no arthritis. Finally, attention hardly needs to be drawn to the correspondence of the results of the individual interview and the physician's similar inquiry at the start of his examination.

In Fig. 1, one can see at a glance the three most important findings. They are: (1) the wide distribution of positive answers to the arthritis and rheumatism question in every severity category; (2) over one-third of the persons with classical arthritis respond negatively no matter who asks the question; and (3) the individual interview situation produces more complete and somewhat more reliable answers than does the household inquiry.

DISCUSSION

There are many interesting facets to the differences observed between the results obtained in the three interview situations. It is not our present purpose to discuss these in detail, for we have little specific information as to the causes for these differences. Two points seem to be of sufficient interest to call for comment. First, there seem to be four differences between the household interview and the individual interview, i.e., the household respondent knows less about other members of the household than about himself, his attention is directed to the several members of the household simultaneously, and his focus is kept moving to new topics, while the focus of the respondent on the individual interview was limited to himself and the single subject of arthritis. Finally, there is the fact that the household question was phrased in the present tense, "Does any member of this household have . . . ?", while the individual interview question was, "Have you ever had . . . ?" The difference between the individual interview situation and the physician's inquiry seems to be that, on the latter occasion, the individuals knew that they were just about to have a thorough investigation for arthritis, so they more frequently expressed their doubts.

There are two principal purposes in making morbidity surveys. The first is to make estimates of prevalence, and the second is to identify cases for comparison with the rest of the population on variables of interest. In relation to the first objective, the principal conclusion concerning the use of the question investigated in this paper is that prevalence rates based on the answers it elicits are difficult to interpret. The data indicate that the question used on a household morbidity survey would lead to a prevalence estimate of 75 per 1,000. A similar question used on a personal interview leads to an estimated prevalence almost three times as large, 209 per 1,000. In neither of these cases is the correspondence with an independent classification of the same persons by a physician sufficiently high to justify any attempt to use them for purposes of precise quantification. Moreover, as soon as one becomes interested in additional variables, one gets into trouble. For example, the estimated sex ratio for positive respondents to the household survey question is

$$\frac{\text{Males}}{\text{Females}} = 0.51$$

while for the cases designated as classical arthritis on examination, it is

$$\frac{\text{Males}}{\text{Females}} = 0.73.$$

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It is not unreasonable to suppose that one would find similar discrepancies if one made comparisons on other variables, such as socioeconomic status or place of residence, from an interview estimate and an examined sample.

Much of the difficulty here stems from the fact that the terms "arthritis" and "rheumatism" are not sufficiently clearly defined, even in the minds of the rheumatologists. It should, therefore, not be surprising that survey respondents are imprecise in their use of these terms.

The weight of evidence in this paper suggests that much more research is needed in the field of measurement of chronic disease morbidity by interview surveys. Some of this research is presently in progress. New and improved questions must be devised, interview techniques must be improved, and perhaps our objectives should be modified toward symptoms and disabilities in preference to specific diagnostic categories, in order to permit preparation of estimates whose validity can be supported.

SUMMARY AND CONCLUSION

1. The relationship between the answers to essentially the same question about arthritis and rheumatism in three different interview situations, and the classification of the same persons by medical examination has been studied.

2. From the data presented, certain estimates of the prevalence of "arthritis and rheumatism" in the Arsenal Health District of Pittsburgh can be made. The definitions used are somewhat arbitrary, and should be kept in mind when making comparisons with other data.

3. The correspondence of answers to interview questions about arthritis and rheumatism, with medical classification, is not sufficient to warrant confidence in prevalence estimates based solely on the answers to these questions.

4. The dangers inherent in trying to study the relationship between arthritis and other variables from interview data have been pointed out.

5. It is recommended that future large-scale morbidity surveys begin with pilot studies similar to the one reported here in order to determine the appropriateness of the proposed questions and interview techniques for the objectives in view.

We acknowledge the assistance of each team member and wish to express appreciation for the special contributions made by D. G. Horvitz, I. Sissman, R. Balk, and M. Wieland.

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FURTHER OBSERVATIONS ON THE DIPHENYLAMINE (DPA) REACTION AS AN INDEX OF INFLAMMATION

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THERE is no specific test for rheumatic fever. Neither is there a test which demonstrates with certainty whether the rheumatic process has become inactive during therapy. There are, however, several tests which indicate the degree of rheumatic activity and which reflect the intensity of inflammation.[1] Furthermore, in the absence of treatment, these tests may indicate that the rheumatic process has become quiescent. For supplementing clinical observations the erythrocyte sedimentation rate (ESR) has proved a useful aid for more than a quarter century.[2] Recently, the "C-reactive protein" (CRP) test has been made available commercially by Schieffelin and Company.[3] Coincidentally, the diphenylamine (DPA) reaction has been used as a laboratory guide in the care of rheumatic patients[4] and in experimental work[5] at this Institute. Others have reported that the DPA reaction is useful in the differential diagnosis of disease.[6]

It is generally agreed that whereas the ESR has been of great value as a guide in the treatment of rheumatic fever, it lacks the sensitivity required to reflect mild rheumatic activity. Smoldering carditis may progress insidiously, escape clinical recognition, and may even lead to heart failure without inducing a significant rise in the ESR. Furthermore, this can occur even in the presence of apparently adequate treatment.

There is need for an accurate test sensitive enough to detect the presence of any rheumatic inflammation. This is particularly true now that: (a) surgical interference for mitral stenosis is frequently advised; (b) ACTH or cortisone are being prescribed in large amounts and for long periods of time. These drugs can be given with relative safety and presumably in amounts sufficient to inhibit completely, that is, *suppress all rheumatic inflammation.* This is the goal in the treatment of the rheumatic patient. But this goal is seldom attained because the amount of an anti-inflammatory drug required is unknown. The optimum dosage of these drugs probably varies with each patient and each attack. In

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general, treatment is administered to a degree sufficient only to induce relief of symptoms and a progressive fall in the ESR. But during therapy two facts are frequently overlooked: (a) at times the disease process may be active and may continue to induce rheumatic lesions but may be undetected; (b) at other times the intensity of the disease, which is cyclic, increases to a degree sufficient to manifest itself clinically. This is called an "escape." A sufficiently sensitive test should supply information on these two important points; for example, indicating that (a) suppression of rheumatic activity requires the administration of an increase in the dose of an anti-inflammatory drug; (b) a cyclic increase in rheumatic inflammation is in progress with a clinical relapse imminent.

Certainly the diagnosis and management of rheumatic fever will be aided by any test sensitive enough to rule out the presence of rheumatic inflammation. The ESR and CRP tests, although of much value, may not always meet this requirement. On the other hand, the DPA determination, or some modification of it, which in experimental anaphylactic arthritis reflects the presence of mild inflammation, may prove adequate. The purpose of this report is to re-evaluate the method and the calculations for the DPA test described in previous papers[4,7] and to recommend certain changes in its practical application. In this study, four DPA calculations will be compared with the CRP determinations made on aliquots of the serum samples and with the changes in the clinical state of the patients as observed by one of the authors (R.C.B.).

CLINICAL MATERIAL

This study concerns itself primarily with an outbreak of rheumatic fever. Most of the patients, young males, developed rheumatic fever between February and June, 1955, following an epidemic of group A, type 19 hemolytic streptococcal infections of the upper respiratory tract. This group of U. S. Navy recruits was treated in two wards of the Great Lakes Naval Hospital. In general, cortisone and/or salicylates were administered to all patients, nearly all of whom were cared for by one physician (R.C.B.). Most were admitted at the onset of the rheumatic attack; a few were transferred from other military facilities. Included were a few patients with other diseases: rheumatoid arthritis, tonsillitis, hepatitis, and Reiter's syndrome. For making comparisons with the findings on these young male adults, a few rheumatic children (girls and boys) treated at the Cook County Hospital were also studied. They were treated in a similar manner. In general, two blood samples were obtained during the height of the attack; another was obtained during subsidence; a fourth sample was obtained in most instances prior to or following discharge from the hospital or during an exacerbation which manifested itself late in the illness. In addition, serial determinations were made on 30 of the Navy and civilian groups. These patients were bled at 48- to 96-hour intervals during the acute stage of the rheumatic attack, and weekly while convalescent. All patients received the customary periods of bed rest, and the appropriate laboratory examinations were made as indicated by the clinical state.

METHODS

The technique used for the DPA (color reaction) determination has been described by Ayala, Moore, and Hess.[7]

Composition of Reagents.—The diphenylamine (DPA) reagent was prepared by dissolving 1.0 Gm. of diphenylamine in 90 ml. of glacial acetic acid and 10 ml. of concentrated sulfuric acid. The acid reagent (ABR) had the same acid composition but lacked diphenylamine.

A 5 per cent solution of trichloracetic acid was used to hydrolyze and precipitate protein.

Analytical reagent grade chemicals were used as supplied except that the diphenylamine was decolorized with charcoal and twice recrystallized from water ethanol solution.

Testing Procedure.—Two-tenth milliliter samples of blood sera were pipetted into 5.0 ml. of 5 per cent trichloracetic acid in 25 by 150 mm. test tubes. The tubes were stoppered with one-holed rubber stoppers each carrying a 6-inch length of glass tubing to act as reflux condenser and placed in a boiling water bath for 20 minutes. At the end of this period the tubes were transferred to an ice water bath and the contents of each tube filtered through paper into appropriate containers.

Two 1.5 ml. aliquots from the filtrate of each sample were transferred and mixed in 18 by 150 mm. test tubes with 3.0 ml. aliquots of the acid blank reagent (ABR) and the diphenylamine reagent (DPA), respectively. The tubes containing sample and acid blank reagent (ABR) or DPA reagent were capped with glass marbles to minimize evaporation and placed in the boiling water bath for 30 minutes.

At the end of this reaction period the tubes were transferred to an ice water bath and cooled.

An extra reagent blank consisting of 1.5 ml. of 5 per cent trichloracetic acid mixed with 3.0 ml. of the diphenylamine reagent was carried through the boiling procedure to serve as a diphenylamine absorption blank in the spectrophotometer. All readings were made in a model 6A Coleman spectrophotometer at a wave length setting of 530 mμ using the tubes in which color was developed. Readings were made against the trichloracetic diphenylamine reagent control blank.

As an extra precaution against unusual diphenylamine degradation the trichloracetic acid diphenylamine reagent control blank was read against distilled water. In all cases absorption did not exceed an optical density (O.D.) reading of 0.010.

Definitions.—DPA—The color produced by a reaction between the diphenylamine reagent and partially deproteinized serum read at 530 mμ. The supernatant tested contains mucoproteins the level of which presumably is being measured by this test.

ABR—The color produced by the reaction between the acid blank reagent and partially deproteinized serum read at 530 mμ.

DPA—ABR—*The purple color test* as previously reported, the difference between DPA and ABR readings.

DPA + ABR—The sum of DPA and ABR readings.

Calculations.—In previous publications[4,5] the purple color values reported have been those which obtain when the O.D. reading for ABR is subtracted from the O.D. reading for the DPA. The reasons for making this calculation were based on the following observations: It was noted that some color, a brownish-pink tint, was always formed when the acid blank reagent was heated with the trichloracetic-acid treated serum sample, and that its optical density was usually of the order of 0.100 or less. An absorption spectrum of the color showed no sharp maxima but was broad with only the suggestion of maxima in the 450 mμ and the 530 mμ wave length regions. However, since the absorption of the diphenylamine-treated serum gave a pronounced maximum at 530 mμ, it was agreed that this reaction had some degree of specificity. The illusion of specificity was heightened by the observation that when treated with diphenylamine reagent, a single

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class of proteins, the mucoproteins, gave the purple color reaction with characteristic (visible in small quantities) absorption. Furthermore, with the exception of a few simple sugars, visible purple color was not obtained with carbohydrates. Moreover, it is known that all carbohydrates treated with strong acid in the presence of proteins give rise to humin formation and some color.

Thus, by subtracting ABR (generalized absorption of nonspecific character and due to the effect of acid on all carbohydrate protein materials) from the DPA reading (specific reaction with some general absorption due to the presence of acid) it was thought that a reading related to the presence of some particular substance would be obtained. Finally, the good correlation obtained between the observations on the purple color levels, ESR and the clinical changes in the rheumatic state indicated that the purple color determination was a useful guide.[4]

During the past two years we have attempted to isolate the material in blood serum responsible for the purple color test. In this work we have studied the reaction between the reagent and carbohydrate materials intensively. These studies have indicated that the purple color test was not as selective as we had formerly believed, but only more sensitive in degree to some carbohydrates than to others. Moreover, it has appeared that the 530 mμ absorption was probably the result of a reaction between the diphenylamine and acid degradation products of material involving carbohydrate. It now seems probable that the ABR determination reflects the presence of these intermediates.* The color produced is much less intense than after the addition of diphenylamine.

Furthermore, it now appears that both ABR and the DPA values are a measure of the same materials but in different degrees of intensity. If this be true, high DPA values should be accompanied by high ABR values. An analysis of previously accumulated data obtained in experimental guinea pig anaphylactic arthritis by one of the authors (J.W.H.) showed this to be a fact. Moreover, it is now apparent that by subtracting the ABR value from the DPA value, one is merely making the resultant difference less expressive of the presence of certain substances in serum. The value obtained for either test uncorrected would be a more sensitive index of inflammation. A priori, there was no reason to indicate that either of these reactions might be superior to the other in reflecting the intensity of the inflammatory process. Therefore, it was necessary to determine whether either the DPA or the ABR value, or even the sum of the two, is the most sensitive reflection of rheumatic inflammation. To obtain this information, a comparison has been made between these values and the CRP determinations done in parallel but by two different laboratories on aliquots of the serum samples. Independent clinical observations were made and recorded prior to tabulation of the laboratory data.

C-Reactive Protein (*CRP*).—The presence of C-reactive protein in the sera was determined by precipitin technique in capillary tubes with the aid of specific antisera obtained from the laboratories of Schieffelin and Company and using

*The accumulated observations on these points are being published by Hess et al.[8]

the procedure outlined in their brochure.* Any evidence of precipitin formation was classified plus.

Determination of Normal Color Reaction Levels.—Serum samples obtained over a period of five years from 45 adults (male and female laboratory workers) in apparently good health were used to determine normal levels for the color reactions. The determinations were made by several laboratories, by several technicians, and in several seasons. Nevertheless, the findings were similar. One member who had had uterine fibroids was consistently higher each year than the other laboratory workers. Results from 45 laboratory workers obtained over a period of four years were combined to calculate normal values. The arithmetic mean was calculated for the DPA readings, the ABR readings, DPA minus ABR, and DPA plus ABR. Standard deviations were also calculated. The normal range for each of these tests was then determined by using twice the standard deviation on either side of the arithmetic mean. There was a normal distribution of values. Under these conditions the boundary limits should include 95 per cent of both the DPA and ABR levels for healthy subjects.

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The normal ranges of optical density for the DPA test, the ABR, their sums and their differences, as found in 1955 for 20 subjects by one technician, were similar to the combined findings of several technicians in previous years for 45 subjects. The values and their ranges are shown in Table I.

TABLE I. NORMAL RANGE FOR COLOR REACTIONS

TEST	20 SUBJECTS (1955)		45 SUBJECTS (1951-1955)	
	NORMAL RANGE	MEAN	NORMAL RANGE	MEAN
DPA	.236–.348	.292	.228–.352	.290
ABR	.027–.067	.047	.023–.067	.045
DPA − ABR	.205–.285	.245	.188–.300	.244
DPA + ABR	.265–.413	.339	.260–.410	.335

RESULTS

Irrespective of year, season, subjects, reagents, technicians, and other variables, there was good agreement for normal values. Prior to evaluating the 761 determinations made on the sera of patients in this study, the following values, obtained from the accumulated data, had been determined to be the upper limit of normal: DPA 0.352, ABR 0.067, DPA − ABR 0.300, DPA + ABR 0.410. Values greater than these were classified as abnormal. Determinations made "blindly" on aliquots showed that during this study the method was accurate to 0.010. The 761 determinations were tabulated under four headings in conjunction with the CRP findings:

a. *Agreement:* CRP positive, all color determinations positive.

b. *Agreement:* CRP negative, all color determinations negative.

*C-Reactive Protein Antiserum-Schieffelin, Schieffelin & Co., 18 Cooper Square, New York 3, New York, 1955.

c. *Disagreement:* CRP positive, some color determinations negative.
d. *Disagreement:* CRP negative, some color determinations positive.

a. Agreement for sera in which C-reactive proteins tested positive and all color determinations were above the normal range (positive): in 211 instances (101 cases) out of a total of 761 there was complete agreement between the test for the presence of C-reactive protein and all color determinations.

b. Agreement for sera in which C-reactive protein tested negative and all color determinations were in the normal range (negative). In 340 instances out of a total of 761 there was complete agreement between the test for the presence of C-reactive protein and all color tests.

c. Disagreement for sera in which C-reactive protein tested positive and some color reactions were in the normal range (negative). This was the case in the following tests:

CRP positive-color reaction negative

1.	DPA	23
2.	ABR	41
3.	DPA − ABR	45
4.	DPA + ABR	21

d. Disagreement for sera in which C-reactive protein gave a negative test and some color reactions were above the normal range (positive). This was the case in the following tests:

CRP negative-color reaction positive

1.	DPA	133
2.	ABR	105
3.	DPA − ABR	96
4.	DPA + ABR	143

CLINICAL APPRAISAL OF THE LABORATORY FINDINGS

Frank rheumatic fever was accompanied by a positive CRP test and elevated color reactions in all cases. As the intensity of the inflammation subsided, either spontaneously or as a result of treatment, clinical symptoms disappeared first and then the CRP test. When serial determinations were made, the DPA and the DPA plus ABR values remained elevated in general from one to twelve weeks after all clinical and other laboratory evidences of inflammation had gone.

The CRP test and "color reactions" were positive in other diseases tested. For example, high values were obtained for rheumatoid arthritis, severe penicillin reactions, Reiter's syndrome, subacute bacterial endocarditis, and erythema nodosum. It appeared that the ratio of DPA to ABR was different in many instances from that observed in rheumatic fever. However, a much larger series of nonrheumatic cases will be required to determine whether the color reactions will be of use in differential diagnosis.

The color reactions, particularly the DPA test, were of value in predicting a rheumatic exacerbation. In each instance it rose prior to or simultaneously with the appearance of clinical symptoms and a positive CRP test. In most of these instances the DPA test had not returned to normal during convalescence. In two cases the DPA value had reached a low level and, even though it rose sharply just prior to the rheumatic exacerbation, it had not yet reached a abnormal level when clinical symptoms appeared and the CRP test became positive. Subclinical inflammation seemed to be reflected in those instances characterized by a positive DPA value, a negative CRP test, and subsequent exacerbation of symptoms.

A few serum samples were from patients with diagnoses unknown. In most instances the color reactions were normal. The DPA test merely indicated a lack of inflammation and was not helpful in establishing a diagnosis.

The 761 serum samples were from 113 rheumatic patients and 30 patients with other diseases or in whom the diagnosis was unknown. The series included 23 in which the DPA value was normal and the CRP was 1 plus. On analysis, it was observed that there were 11 instances in which the DPA was within the range of experimental error but which were classified as normal. There were two instances in which the DPA was rising during an exacerbation but had not reached an abnormal level when the CRP became positive. There were seven sera from patients believed on clinical grounds to have rheumatic heart disease that had long been inactive in which one or two blood samples within a series tested showed a positive CRP. The color reactions prior to and following the positive CRP test were normal in these persons. It appeared that these positive CRP tests in the absence of any rise in the color reactions were probably associated with concurrent acute respiratory tract infections of short duration, and not with rheumatic activity. There were two patients whose symptoms suggested the presence of rheumatic fever but whose final diagnoses remained unknown, who had positive CRP and negative color reactions. In one this occurred in a single instance; in the other this occurred twice. These observations remain unexplained.

The Relation of CRP and DPA Values During Recovery From Rheumatic Fever.—Serial determinations were made on 6 children and 41 adults from the onset of the rheumatic attack to recovery. The cases were selected only on the basis of being typical of acute rheumatic fever. Anti-inflammatory agents were prescribed, increased, decreased, or withdrawn by the attending physicians. It was found that the DPA values in general remained elevated after the CRP test became negative. This was true both for children and for adults.

For example, Fig. 1 shows the fluctuations observed in the six children tested. Treatment varied from relatively small doses of salicylates to massive doses of cortisone (400 mg. daily). With the exception of Case 6, the DPA value remained elevated from one to nine weeks after the CRP test had become negative.

Fig. 2 illustrates patients in whom inflammation subsided promptly and in whom both the CRP and DPA values became normal within 15 days.

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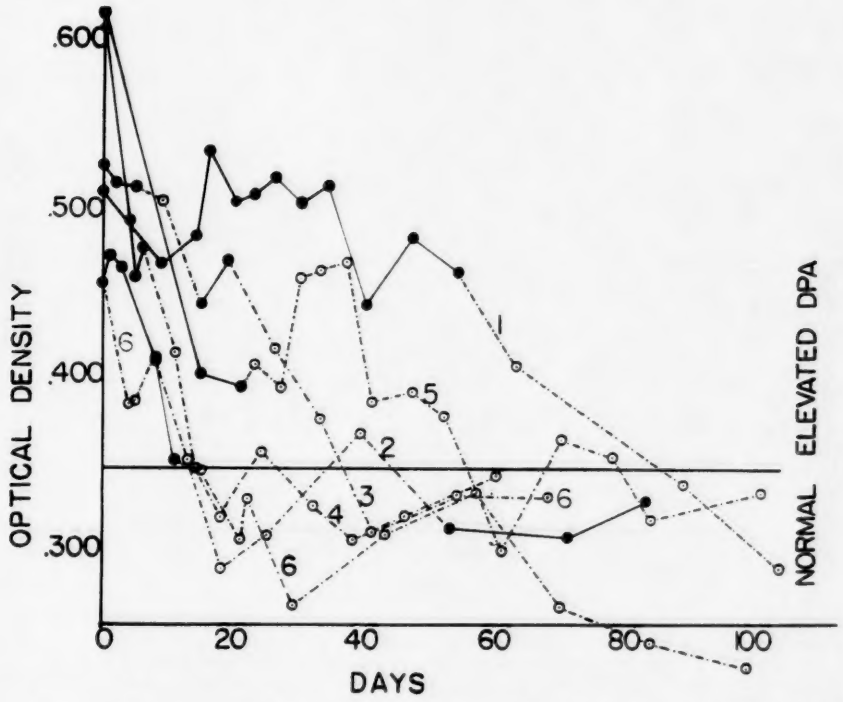

Fig. 1.—Serial determinations in six children with acute rheumatic fever. The CRP was positive from one to eight weeks. In all but one case (No. 6) the DPA value remained elevated from one to nine weeks after the CRP test was negative. Filled circles and solid lines indicate positive CRP tests. Empty circles and broken lines indicate negative CRP tests.

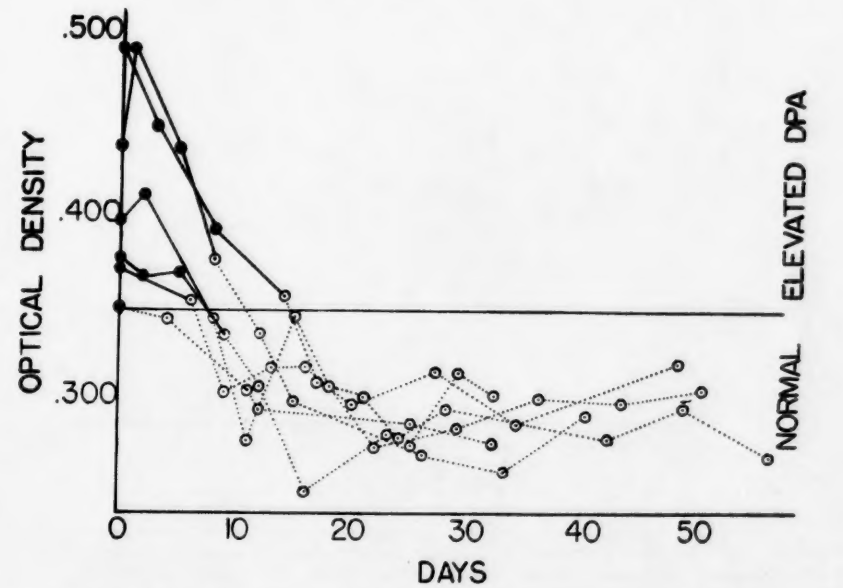

Fig. 2.—Simultaneous and prompt subsidence of both the CRP test and DPA determinations in six adults. Patients in whom both the CRP and DPA values returned rapidly to normal. Filled circles and solid lines indicate positive CRP tests. Empty circles and dotted lines indicate negative CRP tests.

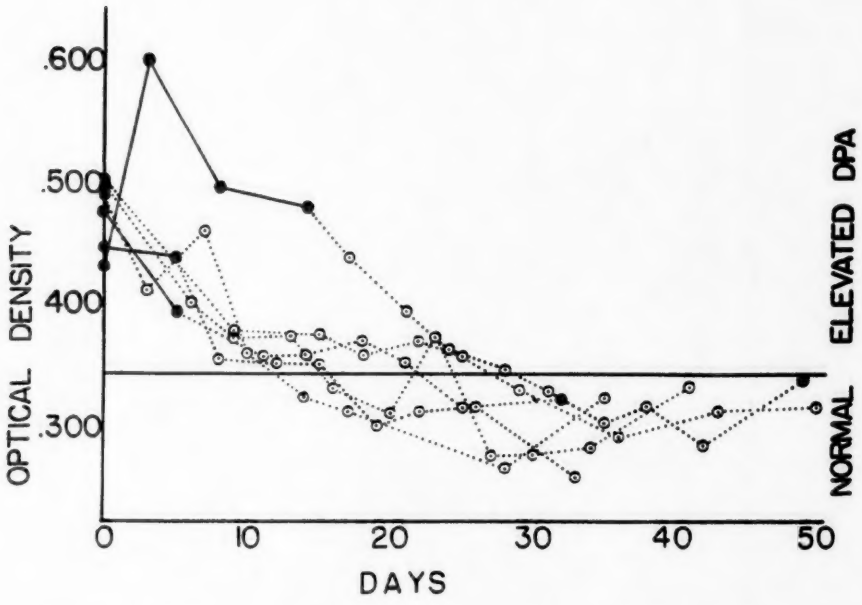

Fig. 3.—Serial determinations on six adults with persistent DPA elevations. Patients illustrating the relatively rapid disappearance of positive CRP test and a persistence for weeks of a positive DPA test. Filled circles and solid lines indicate positive CRP tests. Empty circles and dotted lines indicate negative CRP tests.

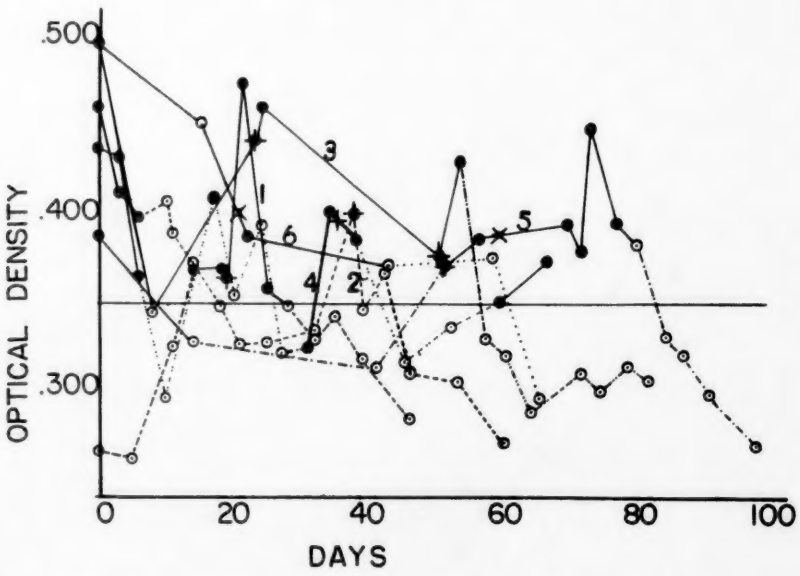

Fig. 4.—Serial determinations illustrating vicissitudes of the CRP and DPA determinations in six patients with rheumatic exacerbations. In each instance the DPA was elevated prior to or coincidental with the exacerbation. Filled circles indicate positive CRP tests. Empty circles indicate negative CRP tests. Crosses point to onset of exacerbation.

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Fig. 3 illustrates patients who became symptom-free and in whom the CRP tests became negative. The DPA determinations remained abnormally high for weeks. There was no evidence of concurrent infection. The most reasonable explanation of these high values was persistent mild inflammation.

Whereas most patients among these children and adults were maintained on adequate doses of anti-inflammatory agents for weeks and escaped exacerbations, there were exceptions. In some instances these exacerbations represented "escapes" with the patients receiving a constant dosage of drug. In other cases the exacerbations followed withdrawal of therapy. Fig. 4 shows that in each instance the DPA rose prior to or coincidental with the recurrence of symptoms. This was not generally true for the CRP test, which, however, became positive in most cases following the return of symptoms.

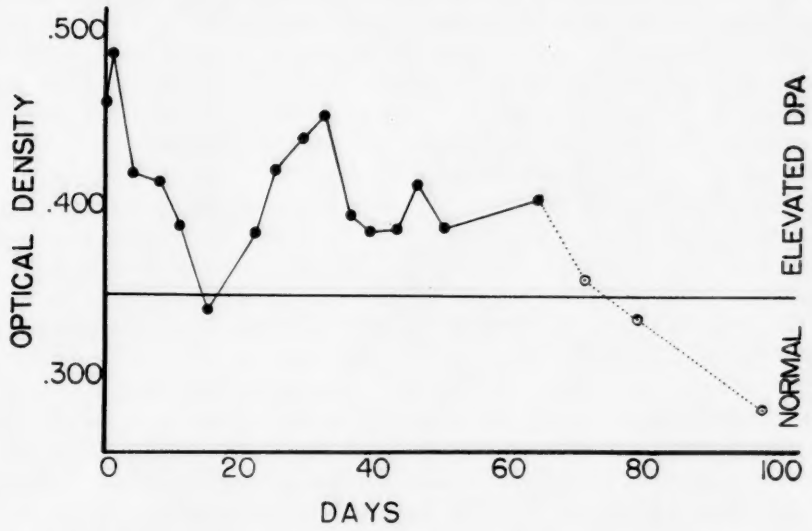

Fig. 5.—Serial determinations on one adult. This patient illustrates continuous rheumatic activity while under treatment. Filled circles and solid lines indicate positive CRP tests. Empty circles and dotted lines indicate negative CRP tests.

Finally, Fig. 5 indicates that even in the absence of frank symptoms, rheumatic inflammation inadequately treated may persist for months. Continuous rheumatic activity of sufficient intensity in some instances was accompanied by a constantly positive CRP test as well as marked elevation of the DPA level.

DISCUSSION

Collaborating with Todd,[9] Coburn and Pauli[10] applied the antistreptolysin O test to rheumatic fever. It was hoped in the beginning of this work on the relation of rheumatic fever to infection that the test might accomplish three things: (a) reflect a preceding hemolytic streptococcal disease, (b) aid in the diagnosis of rheumatic fever, (c) serve as a guide in the clinical management of active disease. This early work, which did not differentiate between antistreptolysin O

and antistreptolysin S,[11] accomplished only a part of its objective. It was demonstrated that the test reflects a preceding streptococcal infection. Furthermore, a low titer in patients who had reached the age of 6 years proved to be strong evidence against the diagnosis of rheumatic fever. However, the titer curve did not serve as a guide in the clinical management of the disease. In many instances, rheumatic activity continued after the ASO titer ceased rising; whereas in other instances the titer remained elevated long after clinical recovery appeared complete.

Later, Kapp and Coburn[12] sought a urine test as an index of rheumatic activity. Subsequently many investigators have studied acute phase reactions and several streptococcal antibodies for this purpose. As pointed out by Wood and McCarty[1]: "Experience has shown that if a sufficient number of antibodies are studied the proportion of rheumatic fever patients showing an unequivocal response to at least one streptococcal antigen approaches 100 per cent." Although antibody studies have strengthened the streptococcal hypothesis, they have not made it possible to determine the point at which rheumatic activity terminates. For example, Coburn and Pauli[13] selected a series of 20 presumably quiescent rheumatic children for splenectomy. They found that nine had elevated antistreptolysin O titers and eleven had normal levels at the time of operation. As a direct sequal to splenectomy the former developed rheumatic attacks and the latter had uneventful convalescenes. No laboratory method was then available to determine whether these nine patients with persistent high antibody titers had subclinical rheumatic activity at the time of splenectomy. Moreover, all subsequent attempts to correlate the titer of streptococcal antibodies with the intensity of rheumatic activity have failed.

For five years cooperative studies have been conducted by several laboratories of this Institute to apply the chemical, *nonspecific* DPA test to the study of rheumatic fever. One objective in this work has been to produce a test which will detect inflammation that cannot be recognized clinically. Recently, an outbreak of rheumatic fever in the U. S. Navy provided an unusual opportunity to re-evaluate the purple color test. It was found that the value previously reported for the purple color determination obtained by subtracting the acid blank reagent (ABR) reading from the DPA reading decreased the sensitivity of the test. Furthermore, it now appears that this subtraction was not justified. On the other hand, it now seems that the DPA determination, uncorrected, is a valid measurement and is a sensitive index of rheumatic inflammation.

The end point of sensitivity of the uncorrected DPA value has not been determined. However, it has been shown that guinea pigs given a mild passive Arthus reaction which showed a minimal swelling of one ankle joint developed a significant rise in the serum DPA value.[5] For example, guinea pigs that had an increase in the mean swelling index of only 2.54 mm. in the left hind ankle joint (ESR and CRP tests negative) had a DPA rise in 24 hours of 0.066. The correlation between intensity of swelling and the uncorrected DPA value was closer than between the swelling and the purple color (DPA − ABR) value. Furthermore, when this monarticular swelling was repeated for three to six days there was a marked rise in the DPA level, comparable in degree to that ob-

served in rheumatic fever. On the other hand, repeated bleedings and mild trauma due to injections of horse serum or egg albumin did not induce a rise in the DPA level. False positive tests were not observed in the guinea pig studies.

The observations reported here again emphasize the importance of subclinical rheumatic activity and the physician's dilemma in recognizing this phase of a disease state. Previous experimental findings and these clinical observations indicate that the uncorrected DPA determination may reflect mild inflammation. Certainly this value is a more useful end point than the purple color value (DPA − ABR) which one of the authors (A.F.C.) has reported in the past. Furthermore, during this study it appeared that the DPA determination may permit the recognition of smoldering rheumatic activity that no longer gives rise to a positive ESR or CRP test. The possibility that the persistent elevated DPA level represents a "false positive" cannot at this time be excluded.

Another unknown is the cause of the rise in the DPA. During these studies it had appeared that this rise may be a reflection of increased mucoproteins in the blood stream. Several investigators[14,15] have pointed out an increase in what they believe to be the mucoprotein blood level in rheumatic fever. No attempt was made in this study to show a relation between these two determinations on aliquots of human sera. This subject has been thoroughly reviewed by Winzler.[16]

To date, the ABR determination has been made merely by the treatment of serum with acid and without attempting to determine quantitative relations. A study of the optimum proportion of acid to serum may afford a more simple, colorimetric determination perhaps even more sensitive than the uncorrected DPA value presented in this report. Further work on simplification and improvement of the ABR determination is in progress.

In conclusion, there is no specific test for rheumatic fever. There is no way to determine with certainty when activity has ended and the quiescent rheumatic state begun. No histologic test is available, and even if there were, one could not interpret with assurance its significance. The best that one can now do is to trace the persistence of inflammation with the most sensitive laboratory method available. In our hands the ESR, the CRP, and the DPA tests are all helpful, and the uncorrected DPA test has appeared to be the most useful in the present study.

SUMMARY

An outbreak of streptococcal infections among Navy Recruits afforded a study of 107 rheumatic fever cases in adults with a wide variety of clinical manifestations.

These 107 cases, of whom at least 81 were associated with a streptococcal epidemic, and six children with acute rheumatic attacks, which occurred sporadically, were observed closely and treated with salicylates and/or cortisone.

In addition to the routine blood tests, parallel DPA and CRP determinations were made on aliquots of blood samples taken at appropriate intervals.

During the period of acute manifestations the four color determinations described in this report were positive. As the effects of treatment or spontaneous

recovery became manifest, the CRP, and the purple color test (corrected DPA level as previously reported) reached normal.

It was observed that the DPA determination, as read directly without correction, remained high for many weeks during convalescence. In fact, it was elevated in 133 instances after the CRP tests had indicated that inflammation had subsided.

In most instances this DPA elevation was interpreted as indicating the presence of subclinical inflammation; in some instances it was the precursor of a frank rheumatic exacerbation.

It is emphasized that an elevated DPA value does *not* necessarily indicate rheumatic fever but is only a reflection of inflammation. Nevertheless, the persistence of an elevated DPA value following a rheumatic attack, in the absence of evidence of infection, may be interpreted as an expression of subclinical rheumatic inflammation. The possibility that the *persistently elevated* DPA level is a "false positive" cannot be excluded but seems unlikely.

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Although nonspecific, this test affords perhaps the most useful laboratory guide now available for the care of the rheumatic patient. For example, it is not subject to certain defects of the ESR. Furthermore, it provides a wide range of values in both good health (0.228 to 0.352) and during inflammation (0.352 to 0.930). Finally, it is an objective, accurate, quantitative measurement.

When the DPA value has returned to normal, one can reasonably assume that rheumatic inflammation either has probably been completely suppressed by a drug or has spontaneously subsided.

If the DPA persists at a high level after a rheumatic attack, one may reasonably assume that fresh rheumatic lesions, which may lead to heart damage, are occurring.

If these observations and their interpretation be correct, treatment should be directed as early as possible in the rheumatic attack to provide a drug dosage adequate at least to suppress all inflammation as reflected by a prompt fall of the DPA value to a normal level. The need remains for a specific laboratory method which will provide an exact end point between activity and quiescence of the rheumatic state.

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THE CONTRIBUTION OF VOLUNTARY HEALTH INSURANCE

II. The Customary Forms of Protection

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New York, N. Y.

*From the Health Insurance Council**

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WHAT are the accomplishments and potentialities of voluntary health insurance toward meeting the financial needs of persons with chronic illness? This article is the second in a series of three directed at answering that question. It deals with the contribution made by the standard or customary forms of health insurance protection.

The initial article in the series, which appeared in the preceding issue of the Journal, furnished fundamental information about the concepts and methods of voluntary health insurance. The final article, which will appear in the following issue, will deal with the broad new form of voluntary health insurance—major medical expense protection—and its promise for the chronically ill.

Before the development of major medical expense protection, voluntary health insurance was commonly divided into four branches on a basis of the hazard insured against: hospital expense protection, surgical expense protection, regular medical expense protection, and protection against loss of income because of sickness or accident. These health-insurance branches are considered in the present article, and, in addition, mention is made of some customary types of health insurance policy that do not fit readily into any of these four categories. Also listed are quite a number of forms of protection, not ordinarily considered as within the scope of voluntary health insurance, which nevertheless are of much financial help to the sick and injured. Moreover, the companies which issue voluntary health insurance are active to some extent in the fields of prevention and rehabilitation, and these topics are discussed briefly.

HOSPITAL EXPENSE PROTECTION

While the growth and development of insurance against hospital expenses were greatly stimulated by the inception of the Blue Cross movement during

*The Health Insurance Council, in whose behalf this article was prepared, is an organization serving to co-ordinate activities of the insurance business with doctors and hospitals in fostering voluntary health insurance. Its membership consists of the associations in the insurance business whose members are insurance companies interested in accident and health insurance. The author, Mr. Kendrick, is regularly on the staff of the Life Insurance Association of America, one of the Council's members.

the depression of the 1930's, insurance companies had been providing a limited amount of such protection for several decades. Back in the early 1900's, some companies had begun to incorporate provisions in their loss-of-income policies whereby the weekly benefit amount was increased by 50 per cent—or sometimes doubled—during any period the individual was in a hospital. This type of policy is still available.

While the extra benefits payable under the early policy forms usually amounted to only a few dollars a day, such amounts were of real help at a time when a private room in a hospital could be obtained at a daily rate of $5 or less.

With the emergence of Blue Cross, the insurance companies commenced broadening their hospital benefits, and providing them in separate policies as well as in connection with loss-of-income benefits. At present, both individual and group insurance protection against hospital charges is very popular and widely available.

Current Policy Provisions.—Modern policies or policy provisions protecting against hospital expense usually offer a benefit both toward meeting the hospital's room and board charges and toward meeting the cost of ancillary services.

Daily room-and-board benefits offered in individual policies range from about $3 to $20. These benefits, formerly payable for about 30 days, are now generally payable for a maximum of 60, 90, 100, or even 365 days. Benefits on account of miscellaneous hospital expenses now usually provide up to ten times the daily benefit, although much more liberal provisions are available.

Group policies ordinarily provide similar daily hospital benefits, usually for up to 31 or 70 days, with durations up to one or two years to be had. The miscellaneous hospital expense benefits of group policies now range from five times the daily benefit to very much larger amounts. In fact, the miscellaneous hospital expense benefits in some group policies are virtually unlimited, which is particularly helpful for patients who require extensive use of costly medical equipment or expensive drugs.

In Blue Cross plans, quite a diversity of benefit provisions is found. Full payment for room and board in semiprivate accommodations is usually provided for either 21, 30, 60, 90, or 120 days, with a 30-day provision the most common. Following the expiration of the full-payment period, the Blue Cross subscriber is usually entitled to a period of partial-or half-benefit days, the partial-benefit period often being 90 days. For ancillary services, full payment is most commonly provided, but partial payment is found in some instances, and for some services no benefits are furnished.

Coverage and Benefit Payments.—At the end of 1954, some 101.5 million persons in the United States were protected against hospital expense, after allowance for duplication. Of the total, 44.1 million persons were employed or primarily insured, while 57.4 million (mainly wives and minor children) were protected as dependents. Fig. 1 shows the distribution of coverage by type of insuring organization (duplication among different types of organization not allowed for).

During 1954 all insuring organizations paid a total of $1,445,000,000 in hospital expense benefits. This total is a new high, representing an increase of 13 per cent over the $1,275,000,000 paid in 1953.

The proportion of total hospital expense benefits paid in 1954 that went to persons with chronic disease is unfortunately not known. However, it was undoubtedly substantial—much higher than might be imagined if account is taken of the benefits paid during the early days of illness to persons whose illnesses prove to be chronic.

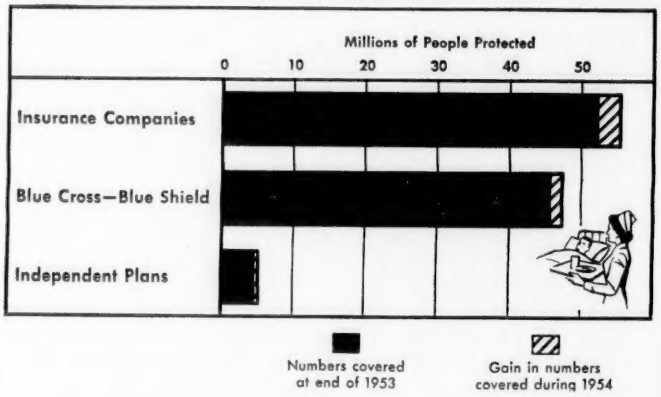

Fig. 1.—Distribution of hospital expense coverage by type of insuring organization.

(Figs. 1-4.—Courtesy Health Insurance Council.)

SURGICAL EXPENSE PROTECTION

As with hospital benefits, policy provisions protecting against the costs of surgery can be traced back to the early 1900's. At that time some loss-of-income policies were broadened to include a schedule of benefit amounts to be paid in reimbursement of the costs of specified surgical procedures.

The effective development of surgical expense insurance, however, may be said to date from 1939, when such protection was first made available apart from loss-of-income coverage. After surgical expense insurance offered by insurance companies began to achieve popularity, the Blue Shield movement was launched.

Current Policy Provisions.—Insurance contracts offering surgical expense benefits usually contain a schedule listing the amount the company will pay in case of specified surgical procedures. For any operation not on the schedule, the contracts usually provide that a benefit will be paid in an amount consistent with the sums that are listed. In both individual policies and group insurance the maximum sum listed, formerly often $100, now generally ranges from $200 up to $500.

Blue Shield contracts are generally similar to the surgical expense policies of insurance companies, except that the participating physicians usually agree to accept the specified sum as full payment for the service rendered, provided the subscriber's income does not exceed a specified amount. At higher income

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levels, cash benefits are usually paid. As with insurance-company benefits, such cash benefits may be assigned and paid to the physician.

Coverage and Benefit Payments.—An unduplicated total of 85.9 million persons nad surgical expense protection at the end of 1954, most of whom also had hospital expense protection. Of the total with surgical protection, 36.5 million persons had primary coverage, while 49.4 million were protected as dependents. The distribution of coverage (unadjusted) by type of insuring organization is shown in Fig. 2.

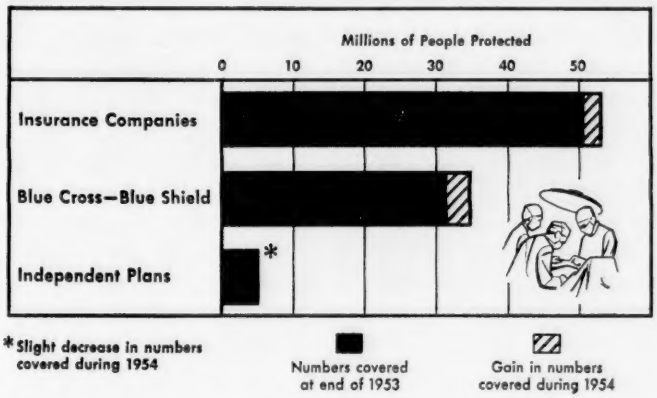

Fig. 2.—Distribution of surgical expense coverage by type of insuring organization.

While figures are not available on the total benefits paid by surgical expense insurance, it is known that in 1954 the total surgical and other medical benefits paid under all forms of voluntary health insurance amounted to $735,000,000, the major part of which was doubtless paid on account of surgery. A considerable proportion of the total sum surely went to persons with chronic disease inasmuch as surgery is often a part of the treatment of such disease, while other medical treatment is usual.

REGULAR MEDICAL EXPENSE PROTECTION

The popularity of surgical expense insurance inspired insurance companies and Blue Shield plans to offer protection against nonsurgical medical expense, often through extension of a surgical insurance contract. Effective developments in this field began about 1944.

Regular medical expense protection—or what formerly was called simply "medical expense protection"—should not be confused with major medical expense protection, the broad new form of voluntary health insurance which will be discussed in the concluding article of this series. Regular medical expense protection, generally speaking, provides benefits only with respect to the cost of the doctors' visits for nonsurgical care. Major medical expense protection, in contrast, ordinarily provides benefits toward meeting almost all types of expense for the treatment of unusually costly (and hence often chronic) illnesses.

Current Policy Provisions.—Three types of physician's calls are distinguished in regular medical expense insurance: in-hospital calls, home calls, and office calls. Many families prefer to budget against the cost of home calls and office calls, where the illness or injury is usually less serious, and to insure only against the cost of in-hospital calls. Consequently, much regular medical expense protection is on an in-hospital basis. However, comprehensive protection is also available, including benefits not only for hospital, home, and office calls but also, in some cases, for the cost of x-ray, laboratory, and special diagnostic examinations.

Typically, $5 is provided for home calls in insurance-company policies, and $3 for office or hospital calls, although there is considerable variance in the amounts provided. Often the first three calls are excluded for benefit purposes, and a maximum limit is placed on the total payments during any one period of disability. Similar benefits for regular medical expense are provided by Blue Shield plans, with full-payment arrangements similar to those in Blue Shield's surgical expense protection.

Coverage.—At the end of 1954 the net total of those with regular medical expense protection was 47.2 million, divided between 21.5 million primarily protected and 25.7 million covered as dependents. Most persons with regular medical expense protection also have both hospital and surgical expense protection. Distribution by type of insuring organization at the end of 1954 is given in Fig. 3.

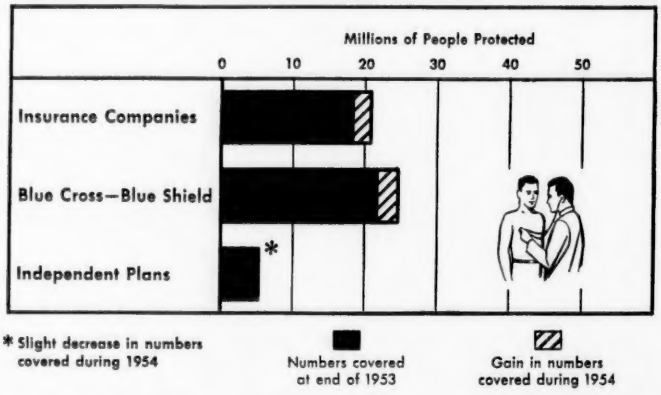

Fig. 3.—Distribution of regular medical expense coverage by type of insuring organization.

Benefit payments in 1954 under regular medical expense coverage are included in the figures given above with respect to surgical expense protection.

GROWTH TRENDS IN HOSPITAL, SURGICAL, AND REGULAR MEDICAL EXPENSE COVERAGE

There has been a remarkable growth in the numbers having hospital, surgical and regular medical expense protection over the past decade or more. The annals of American progress contain few parallels of the record shown in Fig. 4.

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Since the beginning of 1941, the number of persons with hospital expense protection has increased more than eightfold. For surgical expense protection, the number of persons with coverage has multiplied over 16 times. Regular medical expense protection was still in an experimental stage for the first few years shown on the chart, and the number covered increased slowly from about 3,000,000 at the end of 1940 to 3,840,000 at the beginning of 1945. In the ten succeeding years, however, the number covered has multiplied by more than 12.

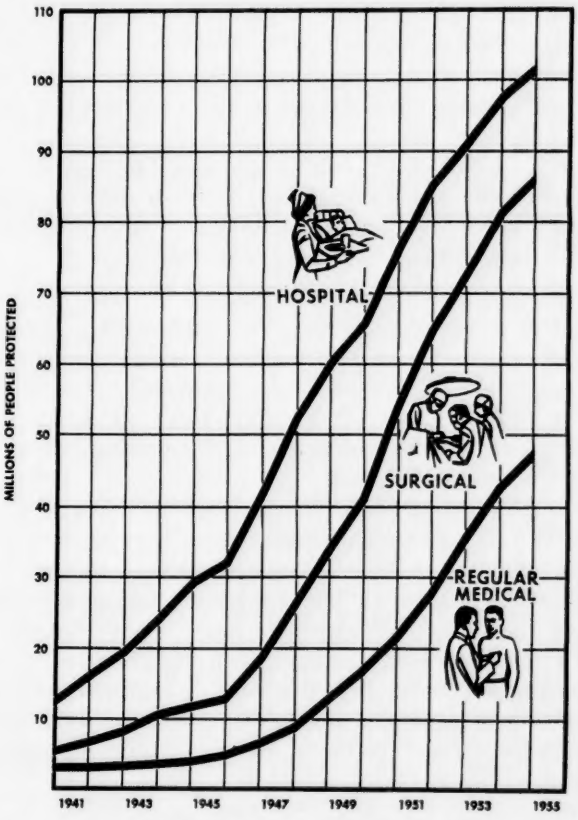

Fig. 4.—Growth of hospital, surgical, and regular medical expense coverage.

PROTECTION AGAINST LOSS OF INCOME BECAUSE OF DISABILITY

Insurance companies offer both individual policies and group insurance providing cash benefits, payable weekly or monthly in replacement of lost earnings, if the insured person is unable to work by reason of illness or injury. Loss-of-income protection is the oldest branch of voluntary health insurance, dating back to the nineteenth century. The benefits of this health insurance branch are of especial value in protecting the family against the risk of chronic illness, and often are partly utilized to pay for hospital and medical care. In fact,

protection of the breadwinner's income is frequently the most important feature of the family's sickness and accident protection, because its basic security is usually dependent on a steady income flow. Obviously, loss-of-income benefits can ordinarily be provided only for gainfully occupied persons.

Current Policy Provisions.—Income benefits under individual health insuranc policies usually commence a week or two after the onset of the illness and may have a maximum duration of one or two years. However, policies are available providing benefits for five or ten years or more for any one illness. These latter, more liberal policies often specify a waiting period of one to three months before benefits commence.

In group insurance the waiting period is usually three or seven days. The benefit duration is usually three months, six months, or a year, but longer durations can be had.

There is no particular upper limit on the weekly or monthly benefit amount in loss-of-income protection, but a reasonable relationship between that amount and normal, full-time earnings must be maintained. And of course, the premium increases with increase in the benefit level of the policy.

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Coverage and Benefit Payments.—At the end of 1954, insurance companies were providing loss-of-income protection for a total of 29.6 million persons, after allowance for duplication. Another 7.9 million persons had substantially similar protection through the paid sick leave plans provided for most civilian government employees and for some employees in private industry. Protection was also furnished for 1.4 million persons through employee mutual benefit associations and union-administered plans.

Together, these forms of protection covered a total of 38.9 million persons at the end of 1954. This figure is exclusive of the unknown millions of employees who have some measure of loss-of-income protection through informal wage-continuation practices of their employers, which do not amount to formal plans. Blue Cross-Blue Shield and the independent health service plans, which furnish other types of voluntary health insurance, do not offer loss-of-income protection.

In 1954 insurance companies paid a total of $540,000,000 in loss-of-income benefits. While many additional millions of dollars of such benefits were unquestionably paid by the other media mentioned above, exact data are not available.

BENEFITS IN AN ILLUSTRATIVE CASE OF LONG-TERM ILLNESS

Loss-of-income benefits are often associated with hospital and surgical benefits in the same policy. To illustrate the benefits that may be paid under a fairly liberal individual policy providing the three types of protection, the case of an insured person hospitalized for 45 days in connection with a major surgical operation can be taken. The convalescence period was ten months. Following are the benefit payments:

For loss of income, at a monthly rate of $300 commencing with the 15th day of disability, i.e., 11 months at $300	$3,300
For hospital room and board, 45 days at $15	675

For miscellaneous hospital expenses, i.e., operating-room fee, anesthesia, laboratory fee, medicines, and other charges	150
For surgical expense	250
Total	$4,375

In addition to the above, if the policy has provided regular medical expense benefits—as is often the case—further amounts could be payable.

OTHER FORMS OF PROTECTION AGAINST THE COSTS OF ILLNESS AND INJURY

There are some types of health insurance which do not readily fit into any of the types discussed so far in this article and which are not major medical expense insurance (to be discussed in the final article of this series). For instance, several million individual and family policies have been purchased which offer comprehensive hospital, surgical, regular medical, and loss-of-income benefits in case an insured person is stricken with poliomyelitis. Polio benefits are also often provided in a group insurance program. And in some instances the policy covers quite a list of so-called "dread diseases."

Again, quite a large number of individual policies of customary type provide special benefits to cover nursing expense. Such benefits ordinarily apply with respect to nursing care received either in a hospital or at home and may extend for as long as 100 days.

More important are a number of insurance and similar types of protection, of much value to the long-term patient, but which are not considered a part of "voluntary health insurance," as the term is ordinarily employed. In particular, the following may be mentioned:

1. *Accident Insurance.*—The insurance types so far described apply to both sickness and accident, although many policies offer more liberal benefits in case of accident than in case of sickness. However, distinct from sickness-and-accident policies, there are some 4½ million individual policies protecting against death, dismemberment, hospital and medical expense, and loss-of-income, only in case of some sort of accident. In addition, some 16 million other policies are in force providing such protection only in case of travel or other specified type of accident. On the group-insurance side, some 14 million persons have accidental death and dismemberment protection. Because serious accidents are much less frequent than serious illnesses, these policy types provide very liberal benefits for quite modest premiums. Personal accident policies offer long-duration benefits (often for life) in specified amounts recompensing for lost income, and they often provide very substantial benefits (ranging up to $5,000 or more) to meet the costs of needed hospital and medical care.

2. *Life Insurance and Annuities.*—About 93 million Americans have life insurance protection. One of the important purposes served by life insurance is to provide a "clean-up" fund to meet such bills as those of the insured person's final illness.

Also, disability income benefits are offered by many life insurance companies in conjunction with individual life insurance policies. One common arrangement of this sort provides a monthly disability benefit of $5 for each $1,000 of face amount of life insurance—the disability benefits being payable without limit on duration. Another common arrangement provides a monthly disability benefit of $10 for each $1,000 of life insurance—the disability benefits being payable up to age 65, at which time the face amount of the policy becomes payable.

Life insurance companies also issue annuity contracts, the benefits of which ordinarily do not commence until the annuitant reaches advanced age.

Because of the prevalence of chronic illness among the aged, a substantial proportion of annuity payments—totaling hundreds of millions of dollars annually—are surely of benefit to chronically ill persons.

3. *Liability Insurance.*—There are many types of liability insurance, including particularly automobile, business, and residence liability policies. Many millions of such policies have been issued.

Among other liability insurance benefits, the injured person may have all his hospital and medical expenses paid and may receive additional benefits in recompense for his loss of earnings. Many liability policies, in fact, provide hospital and medical benefits for individuals injured in the insured person's car or on his premises, without regard to the insured person's liability for the accident.

4. *Workmen's Compensation Insurance.*—Workmen's compensation legislation, usually through insurance written under it, protects about 45 million workers in the United States against hospital and medical expense and income loss, if due to occupational accident or disease. Workmen's compensation insurance policies often provide benefits going well beyond the statutory requirements.

Apart from the workers protected by workmen's compensation, additional numbers of workers are protected against occupational injury or illness by their employers' legal liability. Insurance protection against such liability is often purchased by employers.

5. *Legislation for Cash Sickness Benefits.*—Five programs providing cash benefits in case of lost income due to sickness or disability have been established by compulsory legislation. A Federal program protects railroad workers throughout the nation, while employees generally in four states are covered by state programs.

Some of the laws permit the employer to purchase insurance from an insurance company, instead of participating directly in the government program, provided the benefits for the employees at least meet minimum statutory requirements. However, apart from those with such voluntary protection, there remain about four million persons having loss-of-income protection directly through the legislation.

6. *Government Responsibilities for Medical Care.*—According to a recent Hoover Commission report, Federal responsibilities for medical care include

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specific undertakings to provide completely or partially for about 30 million people. About 4 million persons among the 30 million, mostly active-duty military personnel, are entitled to complete care; and some 3.5 million veterans are entitled to complete care for service-connected disabilities. State and local government responsibilities for medical care, while not so extensive as those of the Federal Government, include the providing of complete medical care for persons in government sanatoriums, prisons, and other public institutions.

In general, it is important to realize that voluntary health insurance is supplemented by the additional types of protection listed above. Collectively, a comprehensive pattern of protection is furnished against the many economic hazards to which human health is subject.

INSURANCE COMPANY ACTIVITIES IN PREVENTION AND REHABILITATION

Two important fronts on which chronic illness or invalidity can be attacked are, of course, prevention and rehabilitation. While insurance operations per se do not call for action on either front, insurance companies have been interested in both and have achieved some notable results.

Insurance Benefit for Preventive Services?—The rather appealing idea is sometimes advanced that health insurance benefits should cover the costs of periodic health examinations, immunizations, and similar preventive services. If such services operated to reduce the amount of sickness, it is thought, the insured persons might enjoy not only better health but also lower premium costs.

While some health insurance policies do provide for diagnostic and other benefits of a partially preventive nature, most insurance companies doubt the wisdom of offering protection against the costs of preventive medicine generally. For one thing, the initial effect would not be to reduce premium rates, and in fact, they might even increase. Premium reductions could not come until later, if and when a reduction occurred in the sickness benefits paid.

In more fundamental terms, insurance cannot render its normal risk-sharing service in preventive medicine, because there is no hazard or risk involved in paying for such items as regular, periodic health examinations. At best, insurance could merely aid the family in budgeting to meet the costs of preventive medicine.

Other Insurance Company Work in Prevention.—While health insurance policies do not generally offer benefits to cover the cost of preventive medicine, insurance companies have engaged in or supported a number of activities in the general field of prevention. Of these, probably the most significant is the work of the Life Insurance Medical Research Fund, which is supported by most of the major life insurance companies.

Since its inception in 1945, the Life Insurance Medical Research Fund has contributed more than $6 million to medical research and to research fellowships. Grants have been made to some 101 institutions, while about 1,300 articles have been published describing results of research. The Fund, whose activities are steadily increasing in scope, devotes its entire resources to work on diseases of the heart and arteries.

Both life insurance companies and other companies issuing health insurance make substantial contributions to medical education and research, other than to the Life Insurance Medical Research Fund. Support is given to such organizations as the National Fund for Medical Education, the American and local Cancer Societies, National and local Tuberculosis Associations, the National Foundation for Infantile Paralysis, and miscellaneous laboratories and clinics for research and teaching.

Among other activites of a preventive nature, insurance companies in their advertising and publicity have for years distributed information on the maintenance and protection of good health and on the avoidance of accident hazards. Similarly, insurance companies—particularly those issuing casualty and fire insurance—have conducted educational campaigns on safety and have done much safety engineering to reduce hazards incident to employment. The fact that the industrial fatality rate today is less than half what it was twenty years ago, suggests that this work has been effective. Life insurance companies have added a great deal to medical knowledge through their analyses of mortality statistics, which have led to important findings on the effect of various habits and impairments upon health and longevity.

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Rehabilitation.—Because individual afflictions and rehabilitation possibilities differ so widely, insurance policies have never attempted to promise benefits to provide for the retraining of the handicapped. Nevertheless, numerous companies issuing workmen's compensation insurance have voluntarily furnished comprehensive rehabilitation services to substantial numbers of persons with permanent or chronic handicaps.

From the inception of workmen's compensation, the insuring companies have seen the economic advantage of making sure the injured workman was offered the best possible medical treatment, often beyond the scope of the statute. However, it was not until about 1930 that it was generally realized that more could be done after the best possible surgical treatment had been furnished. It was then seen that two more stages of care lay ahead for the person with a persisting handicap: Physical training in the art of mastering his disability to the utmost extent permitted by the best artificial devices; and occupational retraining designed to refit him for an independent place in society.

The new thinking led to prompt action. Several companies commenced, systematically, to send injured workmen to recognized, independent rehabilitation centers. Another company not only began to send injured persons to independent centers but also established a clinic of its own to provide certain specialized kinds of therapeutic treatment.

Over the last twenty years, action along the same general line has greatly expanded. One outstanding accomplishment has been the setting up by one company of a fully equipped and staffed rehabilitation center, not only to provide actual treatment but also to serve as a training place for physicians and surgeons and as a pilot project on which similar establishments can be modeled. This center, together with a subsequently established sister institution, has treated over 3,000 severely injured persons—many of them brought from distant cities—

and has returned to independent, useful life approximately two-thirds of those who completed treatment.

CONCLUSION

A look at the cooperative nature of health insurance and its future possibilities may be in order, particularly with reference to financing the costs of chronic disease. The broad possibilities of major medical expense insurance for the chronically ill, however, will be discussed in the concluding article of this series.

Obviously, organizations issuing health insurance do not operate in a vacuum. Policies must be designed to take account of the actual practices and charges of hospitals and doctors. Even more important, policies must be attractive to the insuring public if they are to be bought, and they must be provided at prices people are willing to pay. In group insurance, the desires of the employees and the employer as to the nature and scope of employee welfare program are of determining importance.

These facts mean that future progress in voluntary health insurance is not solely up to the organizations that issue it. While they of course bear primary responsibility for progress, future successes will depend in large measure upon the development of increasingly high levels of cooperation among the various interested groups.

So far as the insuring organizations are concerned, the most important future task is to continue rapidly to expand the numbers having health insurance protection and to increase the adequacy and scope of the benefits furnished. Also, with health insurance increasingly recognized as a necessity, the insuring organizations must continuously strive to provide it at the lowest possible cost consistent with sound practices.

Doctors and hospitals, by the achievements which have made modern medical service of truly lifesaving value, have undoubtedly contributed indirectly thereby to the growing demand for health insurance. Insurance companies as well as the community at large should actively support medical progress. For their part, physicians and hospitals can contribute to the progress of health insurance by cooperating on equal terms with all reputable insuring organizations, thus helping to preserve the free competition which has been so largely responsible for the past progress of health insurance.

Another point concerns the fact that insurance is only a means of bringing together the relatively small premiums of numerous insured persons, with the accumulated funds being used to pay benefits to those stricken by the hazard insured against. In other words, the insurance merely redistributes the funds of those insured; it does not increase the funds. On the contrary, the insurance actually reduces the funds somewhat by reason of the necessary operating costs of the insurance operation. Consequently, there is no reason for those with insurance to be charged more than those without insurance. If those with insurance, who have been prudent enough to try to provide for their health expenses through the advance payment of premiums, should in the end have to pay more

for medical service than if without insurance, then the effect would be to penalize for their foresight those who insure.

Employers have contributed much to the development of health insurance by providing group insurance to their employees and by paying some or all of the premiums. The future development of employee welfare plans can be anticipated with confidence. Moreover, employers can be of increased help in combating the abuses of health insurance in that they are often better able than either the doctor or the insurance company to distinguish between a bona fide and a needless claim for benefits.

The insuring public has made much progress in recent years in learning to use and to benefit from health insurance protection. However, the average family might desirably acquire or exercise greater wisdom in the purchase of health insurance, learning to select accurately the policy that best fits the family's needs. Similarly, families might desirably budget toward meeting their health expenses more than they ordinarily do at present. A special savings account of as little as $100 could be of great value to the average family in eliminating any need for insurance against trivial items, thereby enabling the family's premium dollar to go much further toward providing protection against the more serious, chronic diseases.

In general, the voluntary health insurance movement is a vital, growing thing, absorbing the labor and interest of many persons and organizations. Meanwhile, cooperation among those concerned has been increasing. The continued, earnest efforts of all should enable us to approach the full potentialities of voluntary health insurance, particularly its potentialities as a means of financing the costs of chronic disease.

As companies continue to develop more adequate policies providing more substantial benefits; as more people learn to purchase such policies and to budget against minor health expense; and as companies, doctors, hospital, and others cooperate in preventing unnecessary increases in premium costs, health insurance will come—in much greater measure than at present—to provide the funds to meet the financial needs of those with long-term illness.

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THE CONCEPT OF DISABILITY

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THE development and refinement of techniques for the management of many types of long-term illness, and the realistic expectation of still further progress through research, have created much interest in the widening potentialities for rehabilitation of many patients now disabled.

The group of individuals in society described as "disabled" are of special concern not only to doctors and social workers. Congress enacted the Vocational Rehabilitation Act of 1954, designed to carry out the President's recommendation to strengthen and substantially expand the Nation's resources for the rehabilitation of our handicapped persons. The immediate goals set for the Federal-State Vocational Rehabilitation Program contemplate its progressive expansion from the rehabilitation of sixty thousand disabled persons annually, under the present program, to two hundred thousand disabled persons rehabilitated annually by 1959. This Act, and the appropriation made by Congress for its implementation, emphasize the need for a more concentrated effort to provide the necessary resources through which the physically handicapped may be restored to contributing and personally satisfying roles within the society to which they belong. This forward step is, in part, aimed at the practical matter of effecting some eventual reduction in government spending for the care and support of those who are not now self-maintaining. As physicians and social workers we also prefer to think of this step as reflecting a belief in the worth and dignity of the human being.

For a comprehensive attack on the problems of the handicapped, it is essential for all of us who are in any way related to this important undertaking to examine our own particular attitudes and traditional approaches to the problems of the disabled, and to be willing to undergo whatever reorientation in our "thinking" and "doing" may be necessary.

In this paper, we shall attempt to review some of the central ideas which an interdisciplinary group in Pittsburgh evolved through an examination of the

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characteristics and general nature of the state described as "disability," and through an exploration of the interacting variables which have to be taken into account and handled in a comprehensive approach to understanding and treating this problem as it is encountered in the life functioning of a particular individual or group of individuals. To make these theoretical ideas more meaningful, we shall conclude the article with the presentation of some examples drawn from our own clinical experience and from that of a public agency in our community.

First, we must recognize the fact that the state of "disability" is the result of an interplay of a number of causative factors. Certain of these, such as physical impairment or the lack of specific vocational skills, are rather easily identified. Other, less obvious, factors may escape our notice entirely unless we make an effort to look at the total situation. When these less readily perceived causative factors are not identified and assessed, the effort to modify the disability of an individual may be both unproductive and costly to the individual and to his society.

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We recognize the existing limitations in our knowledge concerning the fullest range of forces which may be impinging upon the functioning of an individual. It is, nevertheless, important to bring together in some systematic fashion the different aspects of our knowledge acquired from a number of sources, including our own professional experience in working with disabled persons.

ETIOLOGIC FACTORS

Analysis of the different factors which we have come to regard as potentially influential in the precipitation or perpetuation of disability suggests that they are related to three general spheres: first, those factors to be found within the individual, himself; second, those factors which stem from the immediate social and cultural environment of the individual and from his different social relationships; finally, those factors which stem from the broader societal and cultural environment. There are obvious risks in breaking down the total situation into these different dimensions, since they are, in fact, closely interrelated. It is necessary to do this, however, in order to discover what each dimension contains.

The personal characteristics and resources of the individual, as he comes under our professional care, represent essentially the result of the dynamic interplay in the past of the individual's constitutional equipment and his special set of life circumstances. Sketching the broad outlines of a profile, encompassing what appears to us to be the essential features, affords a frame of reference for an inquiry and appraisal into the capacities and limitations of a particular individual. For the purposes of this particular discussion, we may have in mind the occupational role of the individual, although it is clear that that is only one of several social roles in relation to which a particular individual may evidence varying degrees of disability. Such a profile must take into account the individual's anatomic and physiologic structure, as these may have been modified or altered by some disease process or physical injury. It must include the general features of his personality structure, his psychologic modes of adaptation and

response, his feelings and attitudes toward himself and others, his own individual strivings and goals as these have been fashioned by his life experience. Moreover, we need to know about his mental capacities, his vocational aptitudes, capacities, and interests, the details of his actual occupational history not only in terms of the kinds of work he has done but also the way in which he has done it, and the gratifications and frustrations he has experienced.

Obviously, the acquisition of such data, which together comprise a total profile of the capacities and limitations of the individual, depends upon a multidiscipline team for its full execution, since no single professional person possesses the necessary range of competencies and skills. It may be impossible to assemble such a team, either because of lack of the necessary financial resources or because it is not possible to obtain the services of all the necessary experts. We must, however, be committed to the actual necessity for such a team, and we must acknowledge that when we are unable, because of the lack of needed professional resources, to engage in a full inquiry and evaluation, conclusions and remedial measures are necessarily based on incomplete information. Because of this, some degree of error may be involved which will adversely influence the outcome of our efforts. In fact, the less complete the team, the more tentative and experimental must be our attitude toward our findings.

Other factors may limit attempts to identify and evaluate all of the causative factors within the individual. We do not yet possess all of the necessary criteria and diagnostic tools actually required in this process, although we are continually adding new and helpful ones to our equipment. Moreover, the individual patient may be limited in his ability to participate in an attempt to study and appraise these factors. In some instances, the limitations stem from attitudes and patterns of operation of the different professional experts involved in the process. The problem may be not so much one of an insufficient range of experts as an inability on the part of the professional persons to acknowledge their actual interdependence in helping people. It is difficult to resist the tendency on the part of the specialist to view the "whole" through the lens of his own specialty. As competent specialists, we must actually possess enthusiasm and conviction about the contributions of our field of expertness. On the other hand, there is always the danger of "specialty-patriotism." Moreover, the attitudes of some members of the different professions suggest that it is difficult for them to work with severely handicapped persons and thus to make the kind of investment of themselves which is required to achieve appropriately limited goals. Finally, there may be an inability to make actual use of currently available knowledge and techniques, either because one is not aware of their existence or because he has not incorporated them into his actual practice.

These limitations do not represent insurmountable obstacles to progress, but they do define the nature of the problems which require attention.

SOCIAL AND CULTURAL INFLUENCES

Turning now to that group of causative factors which stems from the immediate social and cultural environment of the individual and his different social

relationships, attention shifts to the special set of life circumstances with which he is currently interacting. When we refer to the "social situation" of our patients and clients, we must recognize that, while it includes the economic status of the individual, it goes beyond this. It also goes beyond the physical and geographic environment within which the individual lives, although we know that these often influence the nature and degree of certain stresses to which he is daily exposed, and fashion, to some extent at least, the range and character of his life experiences. There are, however, other aspects of the "social situation" which are of special significance because they shed light upon the nature of the forces which either tend to entrench the individual's disability or to promote resolution of it.

The following questions are suggestive, at least, of the lines of inquiry which need to be followed in order to obtain an adequate understanding of the factors which may be operating within the context of the disabled person's immediate social situation.

> Does this individual belong to a primary or "family-based" social group, or is he without such a group? If he is a member of one, to what extent are its supports and interest available to him? What social roles does he have in this group? What psychological roles are implicit in his social roles? What degree of compatibility or incompatibility exists between his socially-determined psychological roles and his inwardly-determined psychological needs? (As, for instance, in the case of a man who by virtue of his social role is the breadwinner of the family, but whose inwardly-determined, unconscious wish may be to be dependent.) Are there special problem situations which arise in his experience as a member of this group? How much of the causation in the creation of these problem situations stems from the individual, himself, and how much from the social realities? To what extent may the social realities have been, in part at least, inwardly determined?
>
> Does this individual belong to other types of social groups, and, if so, what are his actual roles in these groups? What gratifications and frustrations does he appear to experience in these group memberships? What are the prevailing folkways or customs about disease and physical handicap in the various groups to which the individual belongs? How do these influence the perception of him by other members of the group? How do they influence the individual's image of himself?
>
> What changes or alterations in his group memberships and social relationships have occurred as a result of the individual's physical impairment or the disruption of his ability to carry his usual roles? What has been the meaning of these changes for him?
>
> Who are the key persons in the individual's social relationships and what kinds of attitudes do they hold toward him?

The full picture of the "social situation" must take into account the broader societal and cultural environment within which certain other factors may be influential. These factors include the state of the labor market; political considerations; the special sets of arrangements and discriminatory features which govern the distribution of commodities and services, especially those services which are related to medical care and rehabilitation; the status and privileges accorded certain groups within society as, for instance, disabled war veterans;

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the prevailing cultural attitudes and societal response to certain other groups such as the blind, the aged, the mentally defective, the epileptic, and the schizophrenic; personnel policies which tend to undermine the security of workers, resulting in abrupt changes in status and responsibilities; and many other variables too numerous to mention here. In passing, however, we should draw attention to the fact that in many instances it might be possible for mentally defective persons—the epileptic, the arthritic, the palsied, and even the ambulatory schizophrenic—to function adequately if the social environment of these persons could be sufficiently supportive. Unlike the disabled war veterans, whose disability is sometimes re-enforced by an unduly supportive social environment, these persons frequently are accorded more or less an "outcast" status in society.

Simmons and Wolff[1] have indicated that an individual must be seen simultaneously as an *organism* in its physical habitat, as a *group member* in his society, and as a *person* in his culture. They draw attention to the fact that "during a long period of time harmful and helpful forces may blend and balance permitting him [the individual] a workable and safe equilibrium amid many minor fluctuations." "What is most important," they declare, "is the possibility that the scales may be tipped critically at a particular time by a clustering of forces from any one area, or from a triad of environmental pressures, and that, for the individual a landslide of ill effects is started."[2]

It is to be hoped that the social worker's timely aid in the examination, assessment, and modification of the social stresses which interfere with the restoration of the disabled person may, in fact, be the means of avoiding the "landslide of ill effects" to which Simmons and Wolff have referred. To be effective in choosing the most specific foci for his professional effort he must possess sufficient understanding of the actual social forces which are operating in a specific situation. In some instances, the primary effort must be directed toward working with the key persons in the individual's life, or in modifying other aspects of the social environment. Intervention measures, pointed toward specific causative factors in the social environment, may very well supply the corrective procedure necessary for the resolution of the individual's disability. Such well-focused, definitive professional effort, based upon a case by case analysis, is possible only when the social worker has adequate understanding of all the forces in the "social situation" and how they are interrelated.

We have thus attempted to indicate the breadth and complexity of the immediate and broader societal and cultural factors which may precipitate or perpetuate the state of disability. Some of the broader factors we have noted are not subject to direct modification through individual efforts of physicians and social workers. We need, however, to be aware of their influence in the "social situation" of a particular patient or client. As physicians and social workers we must also work toward effecting change in the more detrimental of these sociocultural factors by participating in the social process through which such changes can occur. Moreover, we can work toward the development and further use of social and health planning which will create more adequate resources for the rehabilitation of disabled persons and permit wider accessibility

and better continuity of rehabilitative services. Such programs as the one carried on within the structure of the United Mine Workers of America Welfare and Retirement Fund, or the Work Appraisal Clinics sponsored by the American Heart Association afford substantial evidence of the significance of administrative leadership, comprehensive planning, the mobilization of resources, and the establishment of special arrangements in the actual achievement of rehabilitation goals.

PRINCIPLES OF MANAGEMENT

We have devoted a considerable portion of this paper to a survey of the nature of the multiple causes which, in their interaction with each other, may contribute to the state of disability, because we believe this is a fundamental step in determining the nature of the approach to its modification or resolution. In the light of the multiplicity of causes which have to be taken into account, no one single approach can be valid. It is probable, however, that in any given instance of disability, certain causative factors are exerting more influence than others; therefore it is necessary to determine, on a case by case basis, which of the several causes appear to be central and which ones seem to occupy a more peripheral position in the total situation. Remedial effort directed toward those causes which are especially influential may, as a matter of fact, remove some of the peripheral causes, or at least modify their operation. The important consideration is that an over-all design must be evolved which not only takes into account the various therapeutic resources which are necessary but also suggests the sequence in which certain phases of treatment should be carried out. For instance, it may be inadvisable to subject a given individual to corrective surgery or to involve him in a plan of vocational retraining before he has been given some help with his psychological problems. In another situation, it may be essential to begin with those measures which are pointed toward physical restoration and then to assess the influence of this upon the other variables which have been noted. In yet another situation, the initial efforts should be directed toward some modification of the individual's social situation. It is conceivable also, that the wisest course in a given instance involves the simultaneous use of several different approaches. An over-all treatment design usually reflects several subgoals as well as the general objective. It is helpful to establish both kinds of goals and to evaluate, at frequent intervals, the progress which has been made, in order to recognize the need for change or redirection of the treatment program.

Implicit in the foregoing discussion of treatment planning is the concept that the state of disability is a fluid rather than a static one. A significant degree of alteration in the nature or influence of one or more aspects of the total situation inevitably produces some change in the other causative factors. Thus, frequent reassessment is an essential requirement in an on-going treatment program. It is also a desirable procedure in relation to those instances in which it has been concluded, at some earlier point, that nothing further could be accomplished. We must remember always that new professional knowledge and techniques, expanded treatment resources, significant changes in the labor market, or improvement of the immediate social situation of the disabled individual, as well

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as other changes, may appreciably enhance his capacity to assume contributing and satisfying social roles.

It is desirable, we believe, first to point the study and evaluation process, in a given instance of disability, toward the answer to the question, "What, all things considered, *should* be done?" This establishes the full range of requirements to be met as fully as can be described on the basis of the information at hand. Having answered this question first, we have an adequate frame of reference for determining what *can* be done. The consideration of this question in the light of the first will sharpen our awareness of gaps in our resources and motivate us either to search for them or to develop them in our communities.

Treatment planning of this nature is, of course, dependent upon the use of procedures which will facilitate the process. Communication and collaboration between the different professional experts occur most frequently and advantageously when regular evaluatory conferences are an established part of the procedure. While many of us agree about the desirability of such conferences, we are inclined to let other demands upon our time obscure their actual necessity. In the long run, we usually do not save time by eliminating the conference procedure because we often have to invest even more time at a later point in straightening out difficulties which might have been avoided.

CASE PRESENTATIONS

We want now to present an illustrative case situation, from the files of the public assistance agency in our community, which demonstrates the actual application and use of the principles just advanced.

Within this agency a rehabilitation unit has been established in which one of the objectives is to measure the influence of a comprehensive approach upon the restoration of disabled persons to a self-maintaining status. The visitors were asked to refer those cases in which they believed some possibility existed for restoration of the recipient to an occupational role or to self-help status. These included cases of long standing in the agency, although this was not a requirement for referral. The case loads of the workers in this unit are limited to fifty, and competent supervision is available. These workers have responsibility for the determination of continuing eligibility to receive public financial assistance, but, in addition, there is special emphasis upon the rehabilitative aspects of the case. A careful analysis of the outcomes of this twofold approach is under way, and there is very real evidence that the investment of time and effort has resulted in an appreciable degree of change in a large proportion of the cases which were accepted by the unit.

CASE 1.—Miss W., 45 years of age, had been a recipient of public financial assistance for a period of approximately six years at the time she was referred to this special rehabilitation unit. During the five-month period which followed her referral, twelve hours and thirty-five minutes were expended in helping her. At the close of this period she was not only maintaining herself financially, but also deriving considerable satisfaction from the work itself and from her increased sense of adequacy as a person.

At 2 years of age she suffered complete paralysis of her legs, but later recovered partial use of them, necessitating the permanent use of both braces and crutches, which were supplied by the

Bureau of Vocational Rehabilitation. Although she had expressed actual dislike of her occupation, Miss W. had previously been trained by the Bureau as a furrier seamstress. The Bureau, however, had not been able to place her for employment, and Miss W. had actually had no work experience at the time of this referral. She had an eighth grade education and had taken some typing and shorthand in night school many years before, but this earlier training could not be regarded as a vocational asset. She expressed, however, a strong motivation toward becoming more adequate and self-maintaining. The public assistance visitor carefully examined with her the various work interests she expressed, in an effort to determine which ones might fall within her actual capacities and would be feasible in the light of the various factors which had to be taken into account. For instance, Miss. W. lived at the top of a steep hill and both she and her visitor recognized that transportation would be both difficult and dangerous for her. She expressed an interest in working as a baby-sitter in her own home, but this possibility had to be excluded because of her limited ability to move about. She thought of telephone soliciting as another possibility and expressed not only interest in this sort of activity but also confidence in her ability to engage in it. The visitor agreed with Miss W. about the appropriateness of this possibility and recalled that she knew of such an opening. Later, the visitor learned that this particular opening was no longer available but she devoted some time to a search for another resource which she identified within the community. Miss W. was referred to this agency which subsequently put her in touch with a firm which was looking for telephone solicitors. Miss W. was employed for a trial period on a commission basis and assigned a district in a badly depressed economic area. In spite of this limitation, within one month Miss W. was earning a sufficient amount of money in commissions to enable her to be self-maintaining and, moreover, she was having, for the first time in her life experience, the opportunity to carry an occupational role and to discover that she too could assume this aspect of adult responsibility.

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Although the outcome in this case is striking, it may at first glance appear to represent a rather uncomplicated process and thus not to offer impressive evidence of the usefulness of the principles we have stressed. The inefficacy of vocational training for an occupation which held no interest for Miss W. herself, and which also led her down a "dead-end" street because there appeared to be no demand for furrier seamstresses in her immediate geographic locale, is readily apparent. We can speculate that training as a furrier seamstress had been instituted on the basis of the findings of certain aptitude tests conducted by the vocational bureau which pointed toward the choice of this vocation as the appropriate one for Miss W., but failed to take account of either her own interests or the state of the labor market in the particular community with respect to the employment of people trained for this occupation. In fact, it is pertinent to note that when Miss W.'s actual vocational interests were ascertained, special training was not a necessity. The problem was rather one of finding, through a concerted search, an actual *opportunity* for Miss W. to utilize her *existing resources* in an activity which appeared to be specific to her interests and within her physical and educational competence, and for which there was a need in the community. Once a connection was made between Miss W., with her interests and competencies, and an actual employment opportunity, her disability as far as her occupational role was concerned was rapidly resolved. We have here an instance in which a small amount of appropriate effort and a high degree of ability on the part of the social worker to integrate the variables and to focus her effort supplied an ingredient which had apparently been missing in the previous approaches to Miss W.'s problems as a disabled person.

CASE 2.—Miss J.D.R. was 18 years of age when she came to us for medical treatment in August, 1950.

She related that at the age of 15 years, in 1947, she developed typical Raynaud's phenomena in the hands and feet, which continued unchanged until the following year, when she suddenly developed a febrile illness with joint pains and stiffness for which she was hospitalized. A diagnosis of rheumatic fever or acute arthritis was said to have been made. During this episode she experienced weight loss and weakness, and developed marked deformities of the hands and feet, associated with "thickening and tightness" and brownish pigmentation of the skin over the extremities and abdomen.

As the process appeared to be subsiding, she developed a marked flare of activity of all systemic manifestations and of the articular involvement. She was again hospitalized for seven weeks and discharged, moderately improved, on July 7, 1949. A chronic, smoldering process persisted with moderate progression of the deformities, still largely confined to the hands, wrists, and feet.

Talking with the patient regarding any possible predisposing factors for her illness, she related that in school she was very much attracted to a young man, a student who played first clarinet in the school orchestra. Although she had had no previous musical background, she developed an intense desire to play some musical instrument and, "by chance," picked the clarinet. "The orchestra director read off the list of instruments alphabetically and when he reached 'C,' I decided on the clarinet." She studied and practiced hard, became proficient enough to soon move up to the chair of second clarinetist, next to the young man she admired. Instead of gaining more attention from him, the harder she worked and the more proficient she became as a musician, the less attention her friend gave her. She was competing with him for honors as a clarinetist in a sectional contest when she decided to drop out of the contest "so as not to beat him," for she would have won, "everyone said." Shortly after, the Raynaud manifestations appeared.

The physical examination revealed a pleasant, intelligent young woman, markedly undernourished and with typical stigmata of sclerodactylia, affecting chiefly the fingers, and resulting in flexion deformities at various finger joints, slight deformity at the wrists, and a lesser degree of similar involvement of the toes. The skin over the face, forehead, and distal parts of the upper and lower extremities, was moderately thickened, pigmented, and adherent to the underlying structures. Raynaud's phenomena could be induced in the extremities by emotional stress or by exposure to chilling. Aside from these changes, the physical findings were not remarkable.

The patient was brought to the office by her mother, who assumed the obviously aggressive role in the family, consisting of herself, her husband, and the patient, an only child. The father was a "white collar" worker. The family had always formed a closely knit unit. Within it, the father occupied a passive position in the background, a situation which was accentuated by his daughter's illness.

The patient, intelligent and sensitive, revealed the effects of her constricted family and general social environment. The mother's upbringing, with solid emphasis on "propriety" and disapproval of any show of feeling, was reflected in the frightened, anxious expression of the patient. Her teachers and friends considered her a "sweet girl," who could even be imposed upon without protest.

The chief motivation for the present consultation was the hope of a cure, unrealistically projected by the then current publicity concerning the possible benefits to be derived from corticosteroids in the treatment of "arthritis."

It was clear, however, even from the relatively limited experience of that date, that corticosteroids had nothing of value to offer in this situation.

However, the fact that the patient had weathered two severe bouts of systemic involvement with a diffuse "collagen disorder," still accompanied by vasomotor phenomena in the extremities, without signs of visceral involvement, and with residual changes confined largely to the extremities, suggested the hopeful prospect of some limited degree of physical and functional rehabilitation, provided an extended program of therapy could be carried out. Specifically, the projected program would involve a long period of hospitalization, directed toward improvement of the patient's general physical state and of local changes in the extremities through cervical and lumbar sympathectomies, intensive physical therapy for improvement of the functional capacity of the extremities, and, hopefully, vocational rehabilitation for some gainful occupation.

Some obvious assets, too, were the strong motivation toward recovery, a good psychologic personality base with adequate ego strength, and fundamentally strong family-based support which, with aid, could be utilized to the patient's advantage.

It was clear that the previous status of medical care under "private" auspices would be financially impossible, since hospitalization benefits had been exhausted and cash reserves had been depleted.

The first steps, therefore, involved realistic discussion of the likely treatment program required, explanation of the meaning of medical care on the "house service," of the mechanics of qualifying for it, and social case work help toward acceptance of such free medical care by this family, who had never experienced this before. The response toward this first step hinted correctly at the fundamental resources of the family in accepting realistic pathways for the achievement of specific goals, especially when helped by professional support of the case worker as a member of the clinical team.

Other aspects of the therapeutic situation can only be briefly summarized here, as follows:

The therapeutic attack upon the patient's problem was carried out according to a specific plan by a team, which recognized the difficulties and possible pitfalls, as well as the potentially favorable aspects of the situation. The rapport established with the internist was utilized in establishing him not only as the technical medical expert, but also as the professional counselor, through whom the entire therapeutic program, including all of the patient's and family's questions, was channeled.

Through open discussion and support, case work services facilitated acceptance of various new, strange, and potentially disturbing factors in the hospital environment, as, for example, the composition of the ward population with whom the patient had to live, and unavoidable delays in schedules for surgery. She could express openly her distress over the physical changes she had seen taking place in herself and over the disturbed relationship to her contemporaries. The case worker helped to clarify the place of the "miracle drugs" and their uselessness in her condition, to define the limited goals of physical rehabilitation which had to be accepted, and to differentiate between physical incapacity through deformity and functional aptitude. Through psychiatric and case work help, the patient got a glimpse for the first time of the negative as well as the strong positive features in her social environment, particularly within her family group.

In summary, this girl had an opportunity to recognize that she had feelings, that constant repression of feeling was neither easy nor acceptable to her, that from us she received permission and approval to be friendly, angry, hostile, or rivalrous, as befitted her inclination and the circumstances at any given time. She had the opportunity of actually expressing such feelings to doctors or nurses when it related to delays in surgery, or on exposure to her mother's overprotectiveness, or with regard to her disappointment at being no longer able to play the clarinet.

Once having become freed of the former constrictions in her approach to herself and her demands, she was able to consider the possibility of playing the French horn, in place of the clarinet, as a vocational outlet, which she ultimately developed.

At the same time the mother needed case work counseling as much as the patient. She needed help with the guilt she assumed for her responsibility of having a sick and disabled daughter. She recalled the same feeling in relation to her own mother, who had had tuberculosis and who was, therefore, the object of fear and suspicion in the community. It was helpful when she could face openly the fact that her husband offered very little support and that the burden of making decisions and taking responsibility, as well as the gratification over achievements, would be her own.

She needed help in finding constructive outlets as substitutes for her overprotectiveness of the daughter, which she eventually recognized as being a product of her own anxiety rather than the patient's need. The preoccupation over finding the "miracle drug" for complete resolution of deformity was eventually recognized for what it represented and for the obstacle it could introduce in the way of partial recovery. As the mother developed realistic insight into the problems of the situation, she could transfer more responsibility to us for decisions with regard to sympathectomies and other procedures, the value of which she could not establish herself.

The long period of hospitalization was supplemented by a closely supervised home-care program, during which physical measures of treatment were closely coordinated with supportive psychotherapy and well-focused medical social case work services.

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Thus, through adequate study and evaluation of the total situation, and preparation of the patient and the family for an arduous task of prolonged hospitalization and treatment, it was possible to carry out successfully, over a period of many months, two cervical and lumbar sympathectomies, an arduous physical therapeutic program, and other adjuvant measures of treatment which resulted in marked improvement of the patient's total physical state, much improved functional capacity of the deformed fingers, and, above all, a more adequate adjustment of the patient.

As already indicated, when the patient was ready to consider seriously the choice of a possible career, she recognized the impossibility of continuing as a clarinetist but still saw the possibility of a career in music by playing a French horn, which was well within her functional capacity and which the patient herself had chosen as the most appropriate vocation for her.

When actual testing of this experience proved it to be a realistic choice, and when her teachers and the musical director of a small orchestra in which she played the French horn emphasized her promising potentialities despite marked residual deformity of certain fingers, the patient was referred to the local agency of the State Bureau of Vocational Rehabilitation for scholarship aid to a musical institute, where she is now studying successfully. Fortunately, the Bureau of Rehabilitation was receptive to the concept that serious physical deformity did not necessarily exclude a capacity for functional rehabilitation when the inherent resources of the patient and the family were harnessed to a realistic program of comprehensive medical management.

CASE 3.—J. W., a 41-year-old coal miner who was referred to us by his family physician, had first developed manifestations of rheumatoid arthritis three years before. He responded to chrysotherapy and was reasonably well until a relapse made him unable to work because of severe pain, swelling, and tenderness (typical of rheumatoid arthritis) in the shoulders, both wrists and hands, the knees, and feet. He lost 25 pounds in weight and the laboratory data confirmed the diagnosis of an active rheumatoid state.

The present referral was based on an authorization for comprehensive medical care under the auspices of the United Mine Workers of America Welfare and Retirement Fund, which made the necessary hospitalization possible. Without it such treatment would have been impossible, since the patient was penniless and all the medical resources he required were not available in his community.

Social case work studies indicated a life and family background hardly conducive to recovery from rheumatoid arthritis. The patient left school in a small rural mining community after the second grade, for he "was expected to help support" the family. He started to work "full time" in the mines at the age of 14 years. Throughout most of the twenty-five years of his marriage, there had been severe and almost continuous discord. To escape this situation, the patient, for the past twenty years, had lived alone in a shanty some forty-five miles from the family home. Usually he worked at two jobs, leaving time for only a few hours of sleep. He ate poorly, but contributed regularly to the support of his wife and two daughters, even though he was constantly smarting under the wife's accusation that she was not being given sufficient money.

Despite his need for the protective environment of the hospital and the expectation that he might welcome such a haven, the patient felt guilty about acceptance of it, showed extreme anxiety over his physical limitations, and expressed fears that unless he continued work he would deteriorate and become totally helpless. It was clear that this patient's previous compulsive and exhausting overactivity had been his one means of defending himself against anxiety and his feeling of worthlessness.

Hospitalization, desperately needed under the circumstances, could have proved highly traumatic, if not devastating, to this person if treatment had been limited to physical measures, including the steroids and chrysotherapy which were employed. Supportive case work services which were available to him day by day, along with medical supervision, permitted some release of pressure of his anxiety through open discussion of his problems, feelings, fears, and plans for constructive change. Initially the responsibility for the physical limitations imposed by the treatment program was accepted by the medical team. Gradually, he came to see his overwork and self-deprivation of food, and the subsequent development of his disease, as possibly long-continued reactions to the conflict with his wife. In the case worker and the medical team he recognized for the first time that people, instead of being punitive, can be helpful. That he found acceptance by the medical group, despite his disability, helped to lessen his sense of worthlessness and the need of proving himself to us by overwork.

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Furthermore, it became clear that the general aim of the treatment program was focused on returning him to work at the earliest possible time. This point of view had to be especially emphasized and steps were constantly required to guard against the ever-present potentiality in this instance of precipitating permanent invalidism in a person whose reaction pattern was actually the mask for a basically dependent person. This situation became especially acute when the patient, in a trial of reconciliation with his wife, was threatened by her overprotectiveness upon his return home. This attitude, in contrast to her previously overdemanding one, seemed to underscore to the patient the seriousness of his condition and its probable hopelessness. Thus, as the patient improved, the wife nevertheless insisted that he do less than he was capable of doing. Both attempted to work out their hostility for one another within the milieu of the patient's illness. It soon became clear to the patient, however, that they would be happier separated, and he was able to move constructively toward effecting the separation.

With the guidance of the medical team, in which the case worker played a continuing and active role even when the patient was required to return for frequent follow-up care in the clinician's office, the patient was able to return to work at a pace determined by the actual limitations of his physical disability and the residual activity of the arthritis. Instead of punishing himself and his wife by a debilitating round of physical activity, he increased the hours of work gradually until he resumed work as a mine mechanic on a full-time basis, when the activity of the rheumatic process had largely abated. He has continued at this full-time job with frequent reviews by his local family doctor, periodic consultation with our medical team, and continued supervision by the case worker.

Here, medical management, aimed at preventing disability, was facilitated in the first place by an agency, in this instance the Union-sponsored medical program, without which medical care to this person would have been impossible. The advantages of this facility would, however, have been of academic value only without fullest recognition of the psychosocial factors which could have interfered with constructive utilization of the available medical facilities.

SUMMARY

In this discussion we have attempted to present the fundamental principles that must be taken into account in the evaluation and management of those who are disabled. Through case presentations we have pointed out the actual application of these principles.

The many facets of comprehensive medical care are indispensable attributes of any program which aims to contribute constructively toward the solution of the problems of the disabled in our society.

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HERITABLE DISORDERS OF CONNECTIVE TISSUE

V. Osteogenesis Imperfecta

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HISTORICAL NOTE

SCATTERED reports of this disorder date back at least to 1678.[101] In the early descriptions the disease was usually ascribed to maternal impression. It was said, for instance, that the mothers, while pregnant, saw criminals broken on the wheel or witnessed severe bone-breaking accidents. In 1788 Ekman devoted his thesis at Upsala to the description of this disease in members of four generations in one kinship and presented strong evidence of its inheritance as a dominant. (See Seedorff[101] for an extensive translation of Ekman's original Latin thesis.) Lobstein[75] (1777-1838), gynecologist and pathologist of Strasbourg, wrote on the adult form of this disease in his textbook of morbid anatomy (1833); and Vrolik[121] (1801-1863), Dutch anatomist, described the disease in the newborn infant. Ormerod[88] was early to describe a case in 1859. In 1896 Spurway[107] noted the association of blue sclerotics. In 1900 Eddowes[40] extended this observation and made the significant suggestion that this disease is a "hypoplasia mesenchymialis," a theory for which Bauer,[11-13] Key,[72] and others, including notably and most recently Follis,[45-47] have provided supporting evidence. In 1912 Adair-Dighton[1] mentioned deafness in affected persons, and van der Hoeve and de Kleijn[118] in 1918 clinched this as a bona fide feature of the syndrome.

The terms which have been applied to this syndrome are numerous and include, to mention a few, osteogenesis imperfecta (Vrolik[121]), mollities ossium (Ormerod[88]), fragilitas ossium (Gurlt[58]), and osteopsathyrosis idiopathica (Lobstein[75]). To complicate matters further, the disease is called *la maladie de Lobstein* in the French-speaking portion of the medical world; Eddowes' syndrome (brittle bones and blue sclerae); van der Hoeve's syndrome (brittle bones, blue sclerotics and deafness) and Vrolik's disease (osteogenesis imperfecta congenita).

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Looser[76] suggested the terms osteogenesis imperfecta congenita (OIC) and osteogenesis imperfecta tarda (OIT).

CLINICAL MANIFESTATIONS

Over 50 kinships with at least one affected member have been identified in the records of this hospital, the Children's Hospital School, and the Kernan Hospital for Crippled Children.

The clinical aspects of osteogenesis imperfecta will be discussed under the headings of skeletal, ocular, cutaneous, otologic, and internal. The osseous manifestations greatly outweigh the others in significance.

Clinically two varieties of OI have been distinguished. In so-called osteogenesis imperfecta congenita, the disease is so severe that the relatively minor traumata to which the fetus is exposed in utero produce numerous fractures. The victim is usually born dead or survives only a short time. In the second variety, so-called osteogenesis imperfecta tarda (or tardiva), the manifestations are so mild that blue sclerae may be the only manifestation and fractures may occur only late in life or not at all. (Seedorff[101] further divides osteogenesis imperfecta tarda into levis and gravis types. In the latter, the first fractures are likely to occur when the patient is an infant. In the former, the fractures occur only considerably later.)

The above are artificial distinctions based only on the particularly wide variability of clinical expression in this disorder of connective tissue. OI congenita and OI tarda are fundamentally one and the same disease, the only basis for distinction being that the cases in the two groups are at opposite ends of the bell-shaped curve of expressivity. The foundation for this statement lies in the facts (1) that the two varieties of the disease sometimes occur in different members of the same family; (2) that there is a continuous spectrum of expressivity through the two major varieties; and (3) that the histologic anatomy of the two varieties is qualitatively identical.

On the basis mainly of radiologic changes, Fairbanks[44] distinguishes a "thick bone type", a "slender bone type," and a form he calls osteogenesis imperfecta cystica (Fig. 8,*B*). These, like the antenatal and postnatal distinction which he makes, probably have no basis as far as difference in the fundamental defect is concerned. During prepubertal years a patient may demonstrate an evolution from the "slender bone type" to the cystic type or the "thick bone type."

In summary, *all the several clinical pictures which are referred to in this communication, and which go by separate names in many instances, are one and the same disease which has wide systemic manifestations and an exceedingly great range of clinical severity (expressivity).*

The Musculoskeletal System[20].—As will be seen later, osteogenesis imperfecta is an hereditary defect of bone matrix. Calcification of what bone matrix is formed probably proceeds normally. Osteogenesis imperfecta is then a form of hereditary osteoporosis inasmuch as osteoporosis is defined as a deficiency in the formation (or an acceleration of the breakdown) of bone matrix. This is an important consideration in the understanding of some of the clinical manifestations of the disease and in its rational therapy. For example, in later life,

particularly if few fractures have occurred, the disease may masquerade as postmenopausal osteoporosis; immobilization is as bad for OI as it is for other forms of osteoporosis.

Caput membranaceum and micromelia ("tiny extremities") are the characteristics of OIC (Figs. 3 and 4). The limbs are described as bowed on the chest and abdomen at birth. If the patient survives, the bowing is likely to persist. Chondrodystrophia fetalis (achondroplasia) is often misdiagnosed. By x-ray (see Fig. 4) the skull is likely to show a mosaic pattern in the occipital area as a result of the presence of numerous Wormian bones.[96] This mosaic phenomenon was very striking in the case described and illustrated by Vrolik in 1849[121] (see Plate E of ref. 16). (This was the first case to which the name osteogenesis imperfecta was given.) Caffey states that the mosaic phenomenon occurs in only two conditions: osteogenesis imperfecta and cleidocranial dysostosis (see Fig. 43 of ref. 28 and compare with Fig. 4 here). The diagnosis of OIC has been made at times in utero by means of x-ray.[38] In this form, OI is a lethal or sublethal trait. Death is usually the result of intracranial hemorrhage and other injury since the calvarium offers little protection during delivery and later.

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In OIT, the triviality of the trauma which may cause fracture is well known: fracture of the forearm in whittling or throwing a chip, of the phalanges in writing, of the femora when another person sits on the patient's lap[109] or when the patient stretches out in bed. Apert[6] called these patients "les hommes de verre." Sudden muscle pulls may fracture bones: the olecranon, for instance, has been pulled off by the triceps muscle in swimming[1] or even less strenuous exercise. Relatively little pain tends to accompany the fracture, due probably to the facts that there is minimal soft tissue trauma and that the patients become accustomed to the frequent fractures. Occasionally they learn to set their own fractures.[122] The fractures appear to heal with normal speed but occasionally the callus is so large (see Fig. 8,*A*) as to suggest osteosarcoma.[1,44,73,101,113] However, unlike Paget's disease, malignant degeneration is not recognized as a definite complication of this disease although bone neoplasms have been described.[68,128] Patients (e.g., J. B., in Fig. 6) are sometimes operated on for suspected osteosarcoma. At times overgrowth of bone occurs without evident fracture, and exostosis-like abnormalities develop. (Wide hypertrophic scars occur at the sites of surgical operations such as laparotomy.[97] These may be fundamentally analogous to the hypertrophic callus formation.) Functionally awkward pseudoarthroses may develop. The development of numerous Wormian bones in the occipital area of the skull[96] is a similar phenomenon seen particularly in the "congenital" form of the disease. In the series studied at this hospital, one cannot corroborate, in adults at least, the impression[10] that fracture of the neck of the femur is uncommon as compared with other types of osteoporosis. There is no sex difference in the severity of the fragilitas ossium.

By x-ray all bones have thin cortices and the long bones usually have a slender shaft with rather abrupt widening as the epiphysis is approached. There are instances, as Fairbanks[43,44] has indicated, in which the shaft of the long bones is thick, and yet others in which a cystic appearance is presented on x-ray (Fig. 8). Calcification of what matrix is present is normal.

As in other types of osteoporosis, "codfish" or "hourglass" vertebrae develop as a result of the biconcave deformity produced by the pressure of the normally elastic nucleus pulposus on the abnormally soft bone of the vertebral body (Fig. 7). Furthermore, "schmorlsches Knötchen," actual herniations of the nucleus pulposus into the substance of the vertebral body, may occur. (Schmorl's nodes derive their eponym from G. Schmorl who also did a classical study of Paget's disease of bone [see Section VIII of this series]).

Characteristically the adults have short legs as compared with the upper part of the body. The shortness of the lower extremities is due in part to bowing and to fractures in the shafts of the long bones, but is also due in considerable degree to interference with growth by multiple microfractures at the epiphyseal

Fig. 1.—Seedorff[101] appears to have been responsible for first suggesting that Lautrec had osteogenesis imperfecta. All known facts and photographs such as this are consistent with the diagnosis.

ends of the bones. The short legs with trunk of normal size is unforgettably illustrated by Henri de Toulouse-Lautrec (1864-1901), French painter (Fig. 1). To play Lautrec in the motion picture *Le Moulin Rouge*, José Ferrer walked about on his knees. Marked bowing of the legs often results in a scissors-gait. By x-ray the femurs often assume a shepherd's crook appearance.

Gross deformities, which resemble somewhat those of Marfan's syndrome, such as kyphoscoliosis, koilosternia (pectus excavatum), and pigeon breast, are not uncommon. Arachnodactyly also has been described by several writers.[41,71,90,101] It must be remembered that arachnodactyly is a symptom, not a disease; that its presence does not indicate the coexistence of Marfan's disease. Unequivocal, or at least less equivocal, manifestations of the latter disease, such as ectopia lentis and involvement of the aortic media, have, with rare exceptions,[15] not been reported with osteogenesis imperfecta.

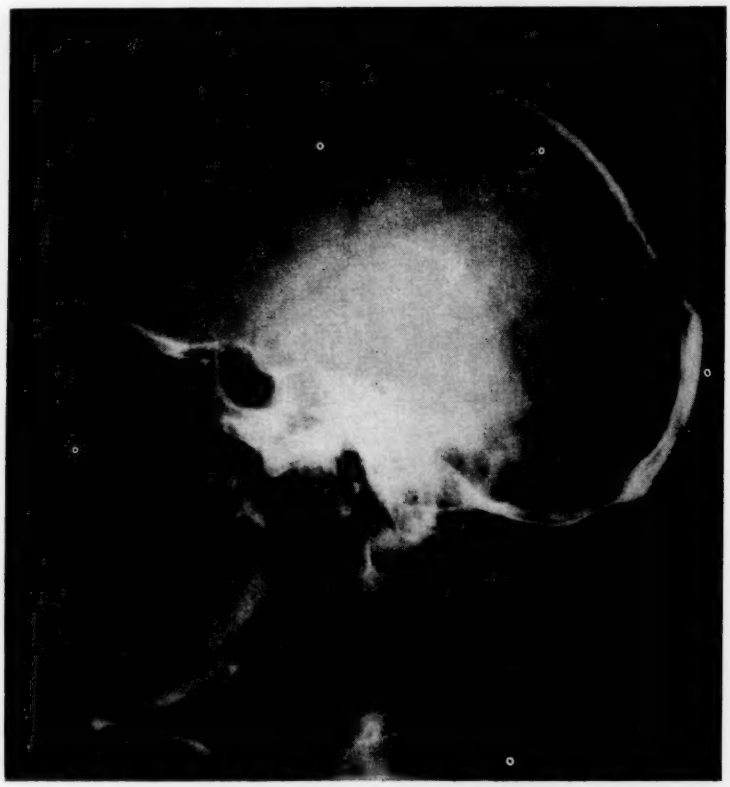

Fig. 2.—"Overhanging occiput" with decrease in the vertical dimension is demonstrated by the skull of this 51-year-old patient (G.I., 587372). She is edentulous. Definite platybasia was judged to be present. The patient has deeply blue sclerae and has had a large number of fractures dating from birth and resulting in marked deformity. She is scarcely taller than a 3-year-old child. Deafness of conduction type dates from the age of 13 years following pertussis and there has been intermittent tinnitus. She has had weakness of the left quadriceps muscle group, with absence of the left knee kick and anesthesia about the left knee, resulting presumably from a compression fracture of the lumbar spine.

The back is usually round and the thorax has a characteristic conical or beehive shape (see x-rays). The face is usually triangular due largely to the bulging calvarium and faciocranial disproportion. The forehead is broad and domed and the temporal areas are overhanging. The "temporal bulge"[37] and the "overhanging occiput"[41] (Fig. 2) are characteristic. The victims have trouble

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getting hats large enough to fit them. As a result of the bulging calvarium, the ears tend to be displaced outward and to point downward. On skull x-ray the inferosuperior dimension is reduced. This, together with the "occipital overhang," the frontal bossing, and the platybasia which may be present in severe cases, results in a mushroom appearance of the skull on lateral x-ray. In general, as with so many other hereditary disorders, victims of this disease tend to resemble each other closely, even though they are quite unrelated. The facies and skeletal proportions are so characteristic that one can usually recognize the victims from a photograph, a feature useful in pedigree investigations.[101]

Fig. 3.—P.D. (A-42000), 3 months old, an instance of so-called osteogenesis imperfecta congenita. Micromelia is striking. The head appears disproportionately large. Numerous fractures were demonstrated immediately after birth. The patient was referred with the diagnosis of chondrodystrophia fetalis, however. The skull bones were described as "crumbly" on palpation. The parents and the parents' families were normal. By the age of 1 year there were evidences of well-advanced hydrocephalus. Death occurred at the age of 38 months.

Because of pelvic deformity, successful termination of pregnancy may be a serious problem.

By x-ray the bones are more radiolucent than normal. Bone age is proportionate to chronologic age.

The teeth are particularly susceptible to caries, are easily broken like the bones, hold fillings poorly, and, although normally shaped, may have an abnormal amber, yellowish-brown, or translucent bluish-gray coloration.[119] Both

deciduous and permanent teeth may show this peculiarity. The lamina dura, as in acquired types of osteoporosis, remains intact. The enamel is thought to be fundamentally normal[14] and the abnormality is thought to reside in the dentine. This prompted Roberts and Schour[91] to suggest the name *dentinogenesis imperfecta* for the dental aspect of this disease, rather than the terms *hereditary opalescent dentine* or *hereditary hypoplasia of the dentine*, which had been used before. Pedigrees in which this was presumably an isolated anomaly inherited as a dominant are described.[66,130] Some of these pedigrees are undoubtedly instances of the generalized disease, osteogenesis imperfecta, in which the dental manifestations dominate overwhelmingly. Roberts and Schour[91] were able to trace a family back five generations to 1763. The dental abnormality was very striking and was inherited as a strict dominant. Of forty-five individuals in five generations, twenty-two were affected. The authors made reference to other evidences of a mesenchymal defect.

The joints are characteristically excessively mobile[18,59,62,101] in this condition, just as in the Marfan syndrome and the Ehlers-Danlos syndrome. It is said[101] that this characteristic is at times so striking that the subject can perform as a contortionist. The basis is in part the presence of weak, stretched tendons and joint capsules and in part the deformity and maladaptation of the bony surfaces of the joints. Grossly, Key[72] described the Achilles tendon in one patient as "the diameter of a lead pencil (0.6 cm.) and translucent in appearance, there being a striking absence of the dense white fibrous tissue usually seen." From the standpoint of histology and of pathologic involvement in a number of diseases, the sclera bears many resemblances to tendon.[51]

Rupture of the inferior patellar tendon may follow exertion with more forceful quadriceps activity than usual.[78,109] Habitual dislocation of joints[9,15,25,64,111,115] or of the patella,[50] pes planus, and pseudoclubfoot[101] are frequent occurrences. The articular laxity probably exposes the victim to falls which are so likely to result in fracture.

Scoliosis may develop as a result of laxity of ligaments as well as of vertebral osteoporosis (Fig. 5). The spinal deformity is often extreme. Pain in the back is frequent in these patients. As in the Marfan syndrome, muscular hypotonia and underdevelopment has been emphasized by several writers.[7,8,35] As in the Marfan syndrome, these features are quite clearly secondary to the anomalies of the tendons and joints and to general debility with reduced muscular activity. The fibrous skeleton of the muscles may be defective, but there is no evidence that the muscle cell itself is at fault. At times, in children (N.T., A46910) enlargement and weakness of the limbs has suggested pseudohypertrophic muscular dystrophy.

Hernia occurs with high incidence in these patients (see Pedigree 603 in ref. 16), as with all the other hereditary connective tissue disorders under discussion, except pseudoxanthoma elasticum.

The Eye.—Blue sclerotics constitute the ocular hallmark of this syndrome. The color of the sclera is described at times as robin's egg blue, at times as slate blue. Of the manifestations of this disease, blue sclerotics are the most frequent.

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Occasionally they are absent in unmistakable instances of the syndrome. This is not surprising since a high degree of variability in severity (expressivity) of this manifestation is to be expected, and overlap with the curve of normal distribution is likely to occur. Impressively blue sclerae are not infrequently encountered in persons free from all stigmata of this syndrome.

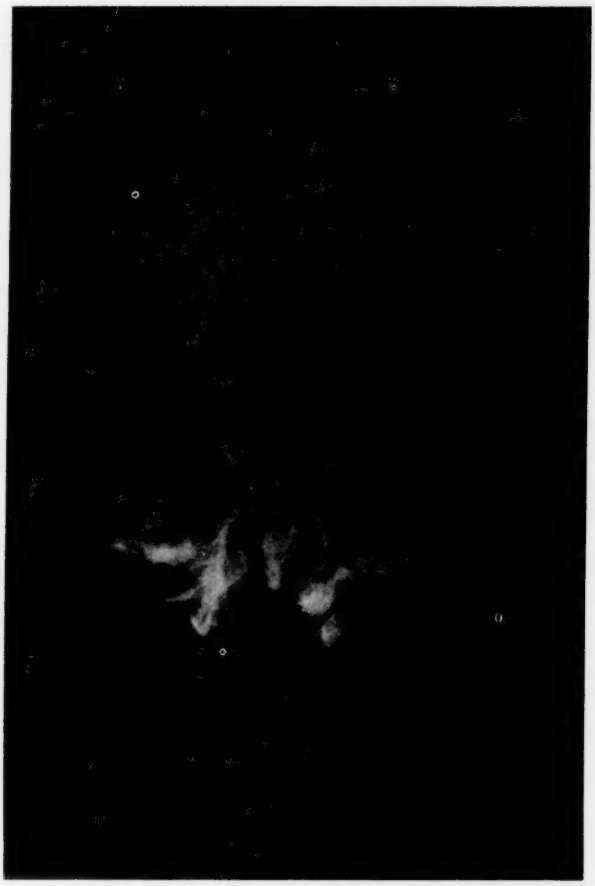
Embryotoxon, a congenital opacity in the periphery of the cornea sometimes called arcus juvenilis, is very frequent.[24,89,92,117,132] By slit lamp the cornea is measurably thinner than normal.[132] Hypermetropia appears to be significantly frequent.[1,2,36,111,112] Chorioretinitis, probably on an independently inherited basis, was reported by Colden.[33]

Other clinical manifestations probably closely related to the same defect of scleral connective tissue are keratoconus,[8,15,26,39] megalocornea,[39] maculae corneae.[120] Behr's patient[15] had ectopia lentis. Premature arcus senilis is described.[120] In two cases observed at this hospital[78] glaucoma has been present. In one it was discovered soon after birth (R.F., 194765) and has been termed congenital; in the other (H.J., 428403) the right eye was rendered blind (phthisis bulbi), presumably by glaucoma, at the age of about 20 years, and the other eye later was affected by so-called chronic, wide-angle glaucoma. There are a few reports of associated glaucoma in the literature.[115,129]

The Skin.—The skin in this condition is characteristically thin and translucent. It may resemble prematurely the atrophic skin of the aged. Healing of skin wounds has been found, by study of surgical incisions in these patients, to result in wider scars than usual.[97] Subcutaneous hemorrhages tend to occur after minor injuries[29] and tests of capillary fragility may be positive.[101] Macular atrophy of the skin is described by Blegvad and Haxthausen.[21] This may be comparable to the spotty blueness of the sclera in some instances.[120]

The Ear.[23,34]—Although the histologic patterns are distinct (v. seq.), the clinical[19,20,25,32,49,99,112,115,118] pattern of the deafness which accompanies this syndrome differs in no respect from that of otosclerosis. Stenvers[110] demonstrated that characteristic sclerosis of the petrous portion of the temporal bone can be detected radiologically even before the impairment of hearing has its onset; and, of course, these changes may be present but not so located as to cause deafness. Deafness may have its onset in the teens, often begins during pregnancy.[48,101] In Nager's patient,[83] hearing loss had its onset at the age of 9 years. As with otosclerosis of other origin, two types, a common stapes-ankylosing variety and a rarer cochlear type, have been described alone or in combination. Therefore, there may be either conduction or nerve type hearing loss. Fenestration operation has been performed in two patients with good results by Shambaugh[102] and in one with indifferent results by Watkyn-Thomas.[125] As with other types of otosclerosis, middle-ear infection aggravates the hearing loss; and deafness may begin in pregnancy. There has been described[110] an interesting blueness of the tympanic membrane, analogous to the blue sclerotics as far as indicating thinness of the structure is concerned. The patient may complain of almost constant tinnitus for long periods and of attacks of vertigo. Labyrinthine disease uncomplicated by deafness has been described.[52,120]

Internal Manifestations.—As for cardiovascular involvement, Sundberg[114] and Johansson[69] have described calcification of large peripheral arteries in victims of OIC. Lobeck,[74] Colden,[33] and Voorhoeve[120] described premature arteriosclerosis. Congenital heart disease was present in one patient.[120] Hass[61] described heart disease in several members of a kinship. From the descriptions of one of the members of that pedigree, rheumatic heart disease seems to have been present in that individual. In general, the heart disease was probably unrelated to the OI.



A.

Fig. 4.—W. B. (A-79352), 2-month-old white male. Radiographic views (*A* and *B*) of the skull in a case of osteogenesis imperfecta congenita, showing a mosaic of Wormian bones and the thin calvarium characteristic of so-called *caput membranaceum.*

In one of my patients (J.G., 149692), with severe S-type rotary scoliosis (Fig. 5), a faint diastolic murmur has been heard to the left of the sternum and there is a borderline increase in systemic arterial pulse pressure. Whether this sound represents regurgitation at the aortic or the pulmonic valve or possibly has an extracardiac origin is unclear.

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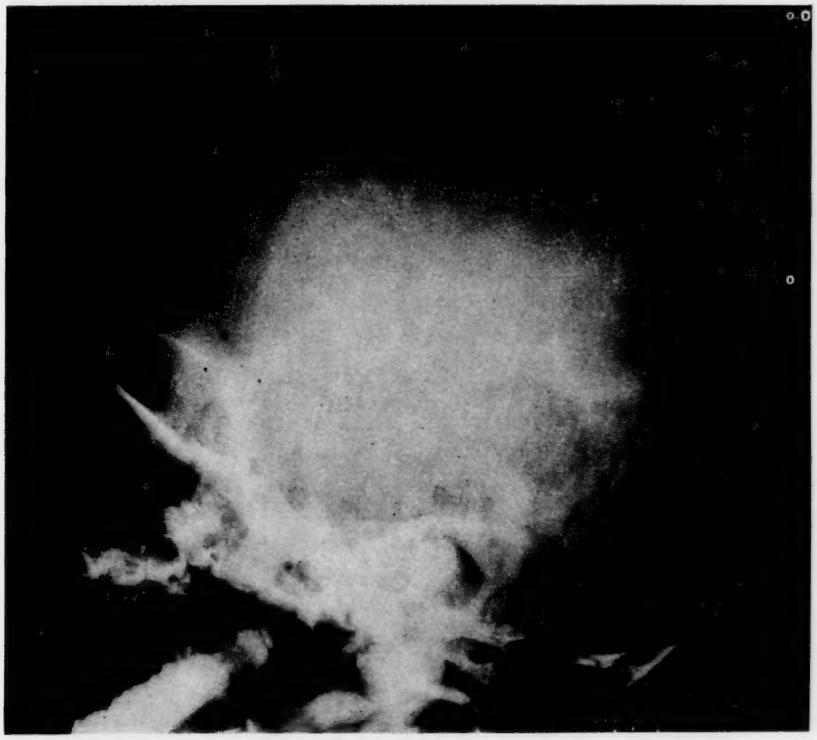
The severe spinal deformity may be followed by kyphoscoliotic cor pulmonale (e.g., C. B., 242806). Premature emphysema is frequent.

There are no pathognomonic chemical changes in the blood. Significant abnormalities of calcium and phosphorus do not occur. Alkaline phosphatase activity is often increased as a result of the multiple fractures.

Neurologic symptoms, particularly those of platybasia and of spinal cord compression, occur occasionally but are usually submerged by the other types of incapacitation from which these patients suffer. Backache and leg pains, which may have an element of nerve-root compression in their causation, are of frequent occurrence. Neurologic deficits attributable to this are less frequent.

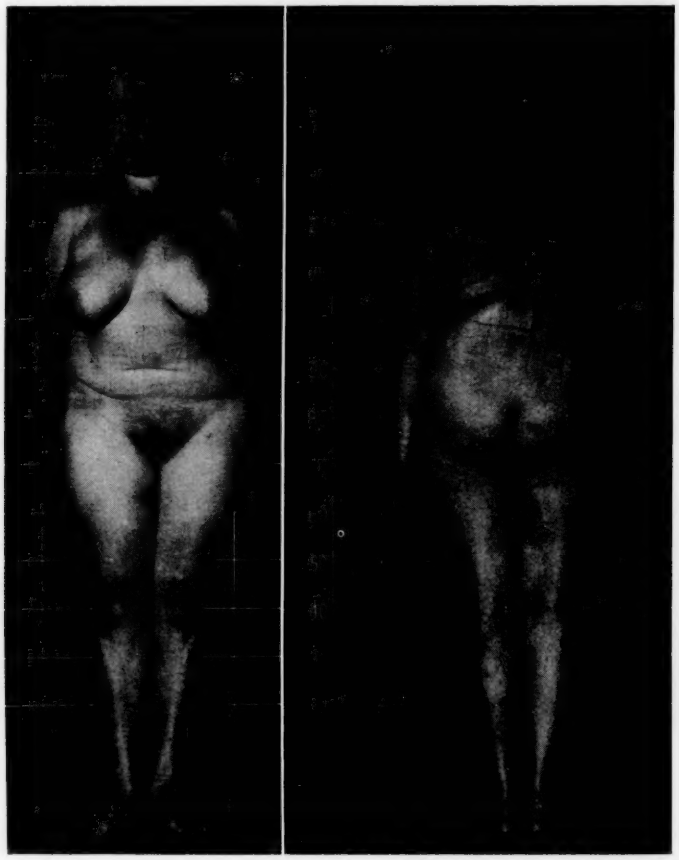


B.

Fig. 4, Cont'd. *(For legend see opposite page.)*

As with idiopathic varieties of platybasia (basilar impression), as well as that due to other bone-softening diseases such as Paget's disease, rickets, hyperparathyroidism, and sarcoid, four types of neurologic involvement should be sought[87]: (1) internal hydrocephalus; (2) bilateral, progressive cerebellar disturbance; (3) interference with the function of the lower cranial nerves; and (4) signs of spinal cord compression at the level of the foramen magnum. The impingement of the odontoid process of the axis on the brain stem is responsible for many of these manifestations.

Two methods are used to detect platybasia radiologically: Chamberlain's line (from the posterior end of the hard palate to the posterior lip of the foramen magnum) normally lies above the entirety of the cervical spine.[30] Such is not the case in platybasia. According to Bull's index,[27] the plane of the axis is normally parallel to that of the hard palate, whereas, in platybasia, the two planes make an acute angle with each other. Plate F of Bell's monograph[16] shows the skeleton of a 12-year-old child with osteogenesis imperfecta and hydrocephalus. The photographs of the skeleton (preserved in the Museum of the Royal College of Surgeons) indicate fairly clearly that platybasia was present and may have been responsible for the hydrocephalus.



A. *B.*

Fig. 5.—J.G. (149692), 43 years old. In *A*, note the bulging calvarium with triangular facies. Flat feet and kyphoscoliosis are also evident in *A* and *B*. The x-ray in *C* reveals the complex spinal deformity present in this patient. The bones are more radiolucent than is normal. The sclerae are deeply blue. Deafness has been present since at least the age of 25 years and tinnitus has often been distressing. Scoliosis was first noted at the age of 13 years, and since the age of 16 years back pain has been a major complaint. The patient is, in general, loose-jointed with flat feet; the head of the humerus was dislocated on one occasion when she was thrown from a bicycle at the age of 7 years. A ganglion on the right wrist was described at one time. X-ray of the skull shows characteristic decrease in the vertical dimension. A diastolic murmur at the left sternal border remains unexplained. An amazing feature of this case of undoubted osteogenesis imperfecta is the fact that *no* fractures have occurred in spite of appreciable trauma on several occasions.

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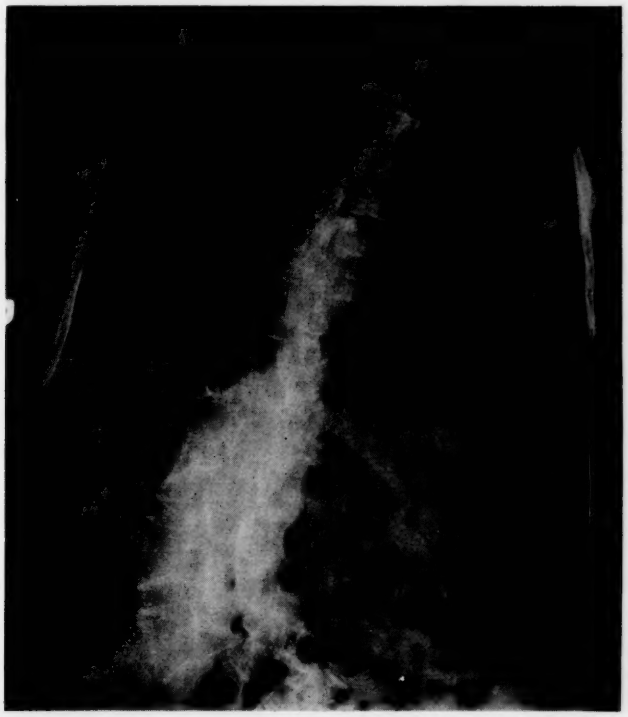
Summary of Clinical Manifestations.—Bell[16] provides entirely credible figures for the incidence of the several manifestations: among adult individuals "with blue sclerotics approximately 60 per cent have an associated liability to fracture, approximately 60 per cent have an associated otosclerosis, and 44 per cent suffer from all three defects." These values might be higher were it possible to eliminate those cases with hereditary blue sclerotics on some other basis. It has not been established that blue sclerotics can occur on an independent, genetically distinct basis and as an isolated anomaly. (They do occur with others of the hereditary disorders of connective tissue.) However, such seems likely from experience with similar situations.



C.

Fig. 5, Cont'd. *(For legend see opposite page.)*

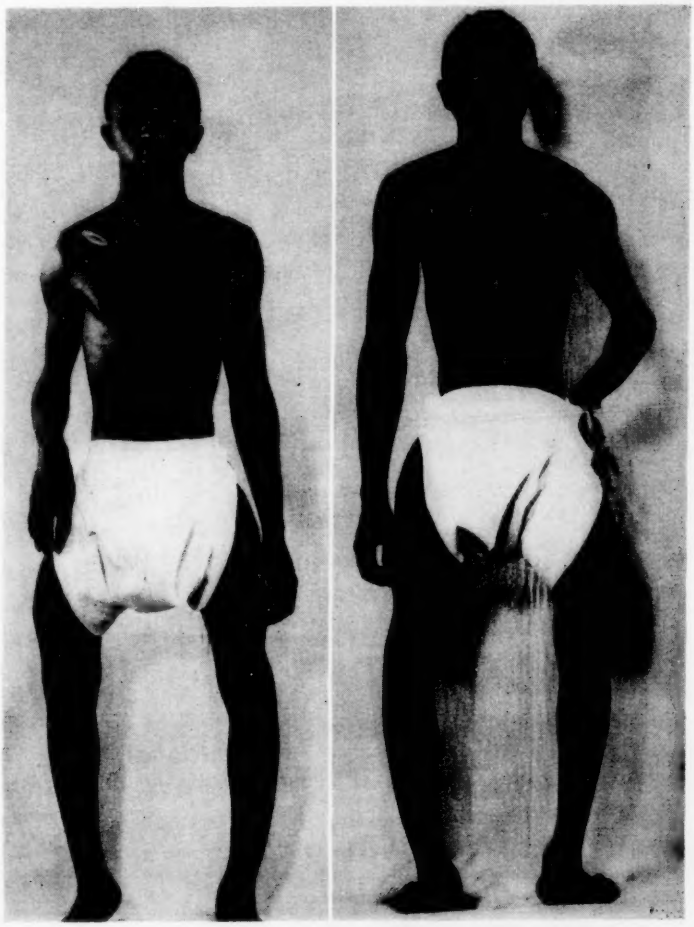
INCIDENCE AND INHERITANCE

Among the five disorders under principal discussion in this series, osteogenesis imperfecta vies with the Marfan syndrome for first place as to incidence. It was relatively easy to accumulate fifty apparently unrelated propositi for purposes of this study.*

There is no peculiar racial distribution of OI, cases having been described in Jews[78] and American Negroes,[56,78,124] and in natives of Japan,[70,84] China,[31] India,[60] Egypt,[7,8] and Russia,[123] as well as all Western European countries.

***Patients from Baltimore or Maryland and patients who have been seen at some time at this hospital have been reported in several previous publications.[45,46,47,63,95,104]**

The evidence is overwhelming that the disease is inherited as an autosomal dominant. Bell[16] found such to be the case for blue sclerotics in 73 kinships with a total of 463 affected persons. In an analysis of 89 families with 1,000 individuals of whom 515 were affected, Fuss[53] demonstrated autosomal dominance for the syndrome of bone fragility and blue sclerotics. One of the best-studied pedigrees is that of a family of the Eastern Shore of Maryland, reported by Hills and McLanahan.[63] Twenty-seven of 51 members of five generations were affected.



A. *B.*

Fig. 6.—J.B. (459707), 21 years old. Bowed deformities of the extremities, flat feet, moderately bulging skull are evident. As a result of the bulging skull, the ears point forward and downward. Beginning at the age of 8 years the patient has had a total of approximately thirteen fractures with no decrease in the incidence of these at puberty. The sclerae are deeply blue.

There is no evidence that osteogenesis can occur on any basis except that of mutation. Seedorff,[101] after studying 55 kinships with 180 affected individuals, constructed a complicated schema based on the theories (1) that each component of the syndrome is the result of a separate gene and (2) that three separate genes

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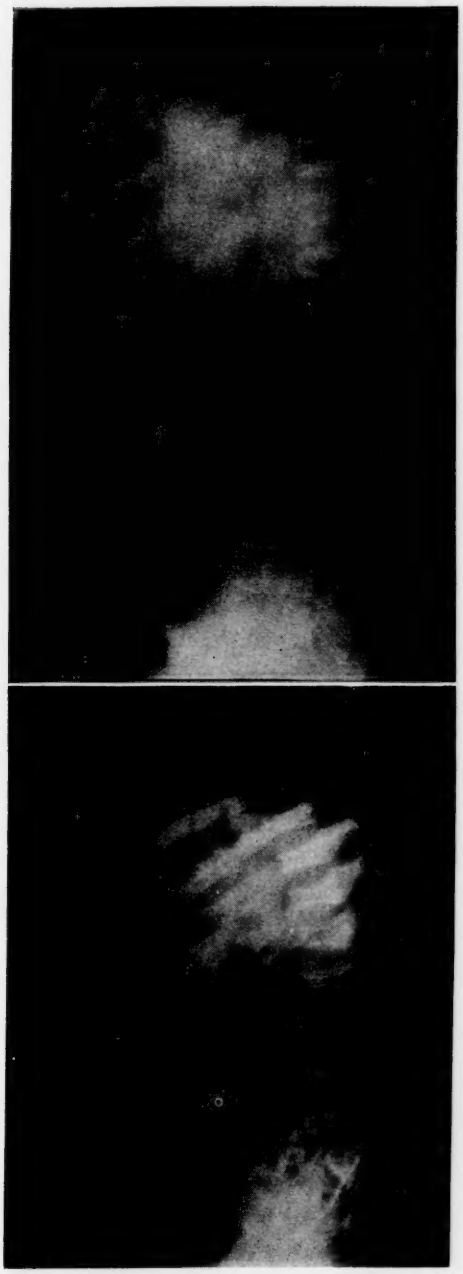
A.



B.

Fig. 7.—Lateral views of the spine in two patients with codfish vertebrae. *A*, Patient J.L.L. (Children's Hosp. Sch.), aged 13 years. *B*, Patient H.R. (Children's Hosp. Sch.), aged 2 years.

control the bone fragility, mutation in one, two, or three being responsible, respectively, for OIT levis, OIT gravis, and OIC. This complex schema is untenable because of the arguments against a multiple gene basis of hereditary syndromes (see Section I of this series) and because of the probability on clinical and histopathologic grounds that the three arbitrarily designated states are in fact different grades of severity of the same disorder of connective tissue.

Frequently the statement appears that the so-called congenital form of the disease probably is not inherited in many instances or is inherited in a different manner (e.g., as a recessive) than the other forms. Many of such instances—severely affected stillborn children of normal parents—may be de novo mutations. I am not aware of the occurrence of two such offspring from parents who were indubitably normal. Even if the parents had to be considered normal by every gauge, suspicion of subtle abnormality would remain. When a severely affected offspring from very midly affected parents is encountered, there is the possibility that both parents are heterozygous and the child homozygous.

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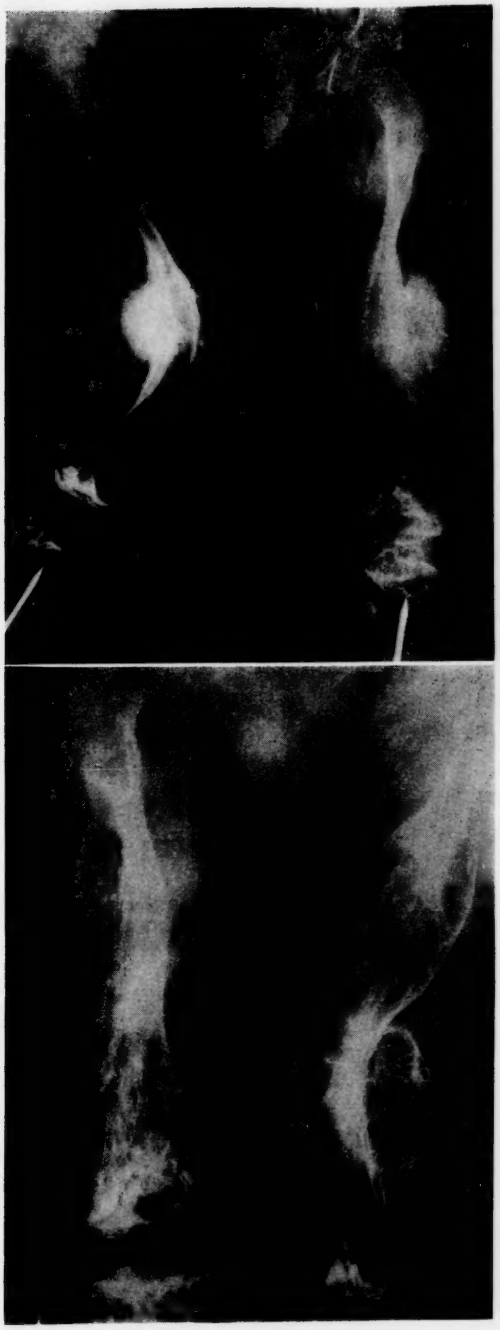
Even with the excellent system for indexing hereditary diseases in Denmark, Seedorff[101] concluded that one is not justified in attempting to calculate the mutation rate for this anomaly. Furthermore, Seedorff could find no conclusive evidence that the parents of patients with osteogenesis imperfecta tend to be older, as seems to be the case in chondrodystrophic dwarfism.[82] In his group of cases of OIT, Seedorff[101] concluded that these individuals are 1.4 times more productive of children than their normal siblings. As far as perpetuating the disease is concerned, each affected individual produced, on the average, 0.75 affected children. If it were not for constantly occurring new cases on the basis of mutation, the disease would in time disappear.

Bell[16] found, in tabulating reported cases of bone fragility with blue sclerotics on the one hand, and cases of bone fragility alone, on the other, a seemingly highly significant difference in sex incidence and mode of inheritance (whether through mother or father) in the two groups. Although the explanation for a basis, if such was the case, is not apparent, the use of published data rather than those accumulated in a uniform manner by the researcher himself is beset with such pitfalls that it is doubtful that one is justified in concluding, and Bell does not so conclude, that a fundamental difference is involved. On the basis of other experience, it is entirely likely that blue sclerotics and fragilitas ossium of otherwise indistinguishable character can occur as isolated, heritable anomalies genetically distinct from osteogenesis imperfecta. It is, of course, well-known that otosclerosis clinically identical with that of osteogenesis imperfecta occurs even more commonly as an isolated anomaly than as part of this syndrome. This is a situation somewhat comparable to that involved in the ectopia lentis of the Marfan syndrome: the manifestations may occur alone or as part of a complex syndrome.

Consanguinity is not impressively frequent in the pedigrees of OI. In the motion picture *Moulin Rouge*, the screen biography of Toulouse-Lautrec, the country physician, recognizing the boy's malady as one which is frequently hereditary, points out to the parents that they are first cousins and advises their separation. Actually it is likely that the consanguinity had nothing to do with

A. C.



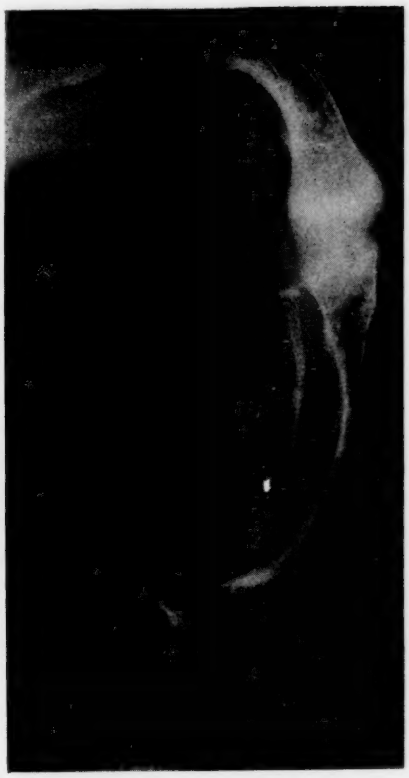


Fig. 8.—*A*, Frontal and lateral views of femur showing hypertrophic callus. *B*, Pseudocystic changes. *C*, Marked curvature of a leg due to bowing both in the femur and in the tibia and fibula.

the son's condition unless both parents carried the disease in very mild form so that there was a chance for the son to have the trait in "double dose," i.e., homozygous form. It is not known that either parent had any stigma of OI.

PATHOLOGY[67]

In the bones, a peculiar, basophilic, periodic-acid-and-Schiff-positive material has been found in place of osteoid. In other tissue, only argyrophilic reticulin fibers and no mature collagen are demonstrated. Histochemically, phosphatase activity is not demonstrably disturbed, epiphyseal cartilage appears to be completely normal,[46] and invasion of the regularly arranged cartilage cell columns by capillaries is normal. The metaphysis shows calcified cartilage but no true bone or osteoid. This calcified cartilage tends to fracture and fragment. Organic bone matrix fails to be deposited and in its stead a peculiar basophilic material makes its appearance. As stated above, the material stains with periodic acid and leucofuchsin and, furthermore, is argyrophilic. Follis[45] suggests that it may represent immature bone matrix in the manner that reticulin, which it resembles in its staining properties, may represent immature collagen.

Swedish workers using recently developed biophysical techniques demonstrated disorganization of the collagen matrix.[17,43] The specific techniques which they employed were microradiography, polarized light microscopy, and x-ray diffraction. Their findings are by no means inconsistent with those of Follis: ". . . in osteogenesis imperfecta the compact bone has a quite abnormal distribution of mineral salts and arrangement of organic fibers. . . . The immature fibrillar bone normally seen in the foetus and newborn infant resembles in several ways the tissue found in osteogenesis imperfecta. Normally this primary bone tissue is rapidly replaced by secondary bone after birth, but in osteogenesis imperfecta this secondary bone tissue is not found."

Osteoblasts and osteoclasts are usually present in normal numbers. Chemically, calcium and phosphorus are present in the bones in a normal ratio; the total content of bone salts is reduced, however.

In the skin, Follis[47] found absence of normal adult collagen fibers and substitution by argyrophilic fibers with other properties of reticulin. The shrinkage temperature of the skin was normal, however.

In the eye, decreased thickness of the sclera has been described as early as 1841 by v. Ammon[5] and more recently by Buchanan,[28] Casanovas,[29] and Follis,[46] but normal thickness was found by Bronson[25] and Voigt.[122] Ruedemann[95] has found histologic changes in cornea and sclera fundamentally identical to those described by Follis[46] in the corium. Clearly, the blue coloration is the result of the brown-pigmented choroid showing through the thin sclera.[127]

In sections of the teeth, "clod-like" calcification of quite abnormal type is seen. Rushton[94] showed that peripheral pulp cells produce "precollagenous" argyrophilic fibers but that these are not converted into collagen except in the immediate vicinity of blood vessels. These observations are in complete agreement with those of Follis, in bone, skin, and sclera.

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Histologically the changes in the ear in osteogenesis imperfecta are quite distinct from those of otosclerosis despite the close clinical similarities. Studies have been made by Ruttin,[98] Gimplinger,[55] and others.

THE FUNDAMENTAL DEFECT

A generalized mesenchymal defect has been assumed for several decades. The recent histologic investigations of Follis (described above) appear to indicate that the fundamental difficulty may be in the maturation of collagen beyond the reticulin fiber stage. (This assumes that one can subscribe without reservation to the view that reticulin fibers are immature collagen fibers.[77] Even if this is not the case, it can be stated that the collagen fibers in OI are abnormal and resemble reticulin fibers in many respects.) As far as the bones are concerned, the disease must be considered a disorder of osteoblastic activity. Normal chondroblastic activity is suggested by the fact that growth and development of cartilage are normal.

It has been claimed by Seedorff[101] that a condition in cattle called anosteoplasia congenita[65] is an identical disorder.

MISCELLANEOUS CONSIDERATIONS

In general, a decrease in the incidence of fractures is observed after puberty with, possibly, an increase in this incidence after the menopause. Both clinical experience in man[4] and experimental evidence from animals[54] indicate an important role of sex hormones in the normal formation of bone matrix. This hormonal influence may explain in large part the observations cited above; increased vigilance on the part of the patient may be in part responsible for the improvement after puberty.

Estrogens and testosterone are worthy of more extensive trial in these patients.[93] Certainly it is important to avoid the superimposition of postmenopausal osteoporosis on the osteoporosis of this heritable disease.[81] Nonmasculinizing forms of androgens[57] can be employed. Serum albumin, which seems to be a percursor for bone matrix, is beneficial when administered to patients with certain acquired varieties of osteoporosis.[3] It apparently has not been used in osteogenesis imperfecta. Strontium has also not been tested,[103] with the exception of one study[22] in which the author thought the results were favorable and rendered further study worth while. As one might expect, all manner of medications have been employed for this distressing and longstanding disorder, for example, thymus extract.[100] Furthermore, because of difficulties in evaluating results, the variable course of the disease, and wishful thinking on the part of physicians and patient, enthusiastic reports have at times been forthcoming.

Unless quite by accident some efficacious therapeutic measure is discovered, no definitive progress in the therapy of OI can be anticipated until the precise reason for the failure of normal development and/or maturation of collagen is understood. Only then can measures directed at correcting the specific deficit be devised. There is every reason to anticipate that the biochemical defect in

hereditary disorders such as this will be precisely defined in the future. Optimism in regard to possibilities of correcting or modifying the basic defect is justified.

As in acquired forms of osteoporosis it is highly important to avoid immobilization of the patient because of the further depletion of bone matrix occasioned thereby. It is doubtful that a high intake of calcium, phosphorus, and vitamin D are helpful, and the combination of these with immobilization may have dire effects: C. B. (J.H.H. 242806) developed large bladder stones and a Proteus infection of the urinary tract after immobilization for eleven weeks in a cast, and a "bone-building diet" which included several quarts of milk a day and added calcium and vitamin D. The pinning and plating of fractures have much to recommend them because they reduce the necessity for immobilization. Deformity has been corrected by intramedullary nailing.[79]

Osteotomies and related procedures of orthopedic surgery are employed to correct deformities.

Pregnancy is not to be encouraged because of the 50 per cent chance of the child being affected and because of adverse effects of the pregnant and parturient[85] states on the skeleton. Deafness from otosclerosis often begins or is aggravated during pregnancy. Because of the pelvic deformities of the disease, delivery may be mechanically very difficult. One patient[78] has fractured her coccyx with each of the deliveries.

Because of inactivity it is easy for victims of this disease to become obese. Obviously, this is to be avoided. In young patients, Froelich's syndrome is sometimes suspected without basis.

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SUMMARY AND CONCLUSIONS

Osteogenesis imperfecta is a generalized disorder of connective tissue involving, in addition to bone, the skin, ligaments, tendons, fascia, sclera, and inner ear. Although the most frequent functionally important manifestations are brittle bones and deafness, blue sclerae are a dramatic feature, and thin skin, loose-jointedness, and hernia occur as manifestations of a single basic defect.

An exceptionally wide range of expressivity has resulted in the description of several different syndromes, all of which are but different expressions of a single type of connective tissue disorder. The disorder is inherited as a Mendelian dominant.

Studies to date are most consistent with the view that the basic defect is one which involves the maturation of the collagen fiber beyond the stage of the argyrophilic, reticulin fiber.

Dr. George O. Eaton, chief of staff at the Children's Hospital School, Baltimore, kindly permitted use of the resources of that institution during this study.

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Special Article

A BIBLIOGRAPHY OF INTERNAL MEDICINE: BRUCELLOSIS

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THE book by Surgeon-Captain Louis Hughes (Ref. 6) is generally accepted as the storehouse of information on the early knowledge of Malta fever. I. F. Huddleson's monograph, *Brucellosis in Man and Animals* (New York, 1943, Commonwealth Fund) contains much useful general as well as bacteriologic information and has a comprehensive bibliography. The monograph by H. J. Harris, *Brucellosis (Undulant Fever), Clinical and Subclinical* (ed. 2, New York, 1950, Paul B. Hoeber) is also to be mentioned. This volume of some 600 pages deals with every phase of the subject; under the heading of "Symptomatology," for example, all the rare clinical phenomena of brucellosis, such as endocarditis, ocular troubles, intermittent hydrarthrosis and others, are described with references to the literature. With regard to the bacteriology of brucellosis, the article by J. T. Duncan, L. E. H. Whiby, and A. D. McEwen in *A System of Bacteriology in Relation to Medicine*, (London, 1930, His Majesty's Stationery Office, Ch. IX, p. 386) is authoritative and comprehensive, as is the section in Topley and Wilson's *Principles of Bacteriology and Immunity* (ed. 3, Baltimore, 1946, The Williams & Wilkins Co., Vol. 2, p. 1692). As to general bibliographies, Hughes' book contains a comprehensive list of references to the early literature (Ref. 6, p. 29) and is supplemented by a compilation of publications from 1897-1907 by J. W. H. Eyre in the British Commission Reports (Ref. 12), Part V, 1907, p. 66. Harris' book contains a list of no less than 742 references.

BRUCELLOSIS

Bacteriology—Refs. 2, 3, 4, 9, 13, 14, 15, 19, 27, 29.
Blood, in—Ref. 36.
Cattle, relation to brucellosis—Refs. 9, 31.

Supported by a grant from the California Foundation for Medical Research.

Clinical—Refs. 1, 2, 3, 4, 5, 8, 10, 20, 22, 31.
Chronic or ambulatory form—Refs. 8, 17.
Diagnosis—Ref. 44.
Epidemiology—Ref. 20.
General—Refs. 1, 2, 3, 4, 6, 12.
Goats, relation to Malta fever—Refs. 16, 18.
Immunology—Refs. 11, 25, 26, 28.
Mode of infection—Refs. 21, 23, 32.
Pathology—Refs. 24, 30, 34, 43.
Serum diagnosis—Refs. 7, 8, 26.
Treatment—Refs. 35, 37, 38, 39, 40, 41, 42.

1. Marston, J. A.: Report on Fever (Malta). Army Medical Department, Statistical, Sanitary, and Medical Reports for the Year 1861, London, Harrison & Sons, 1863, p. 486.

Although it is probable that "Malta fever" had existed for a long time in the Mediterranean basin, the early accounts of fevers in this location were too confused for intelligent classification.* Marston discussed the fevers seen at Malta, and after separating typhoid fever and some others, gives, we believe, the first recognizable account of Malta fever under the designation of "Mediterranean remittent." "By this is meant a fever characterized by the following symptoms and course: A preliminary stage of subacute dyspepsia, anorexia, nausea, headaches, feeling of weakness, lassitude, and inaptitude for exertion, mental or physical, chills, muscular pains; lastly a fever having a very long course—three to five, or ten weeks—marked by irregular exacerbations and remissions, great derangement of the assimilative organs, tenderness in epigastric region, splenic enlargement, slight jaundice, without any exanthem. Neither bronchitis or diarrhoea as a rule. The patient is prone to relapses, and the disorder is followed by a protracted convalescence and a chloroanaemic aspect; very frequently also by rheumatism of some form or other, but without any tendency to lesion of the peri- or endocardial membranes. Pathologically, it is marked by congestion or inflammation, with softening of the enteric mucous membrane, without any lesion of Peyerian follicles, but with hypertrophies of liver and spleen. There is no fever so irregular as this in its course and symptoms . . . Convalescent stage. It is now that the anaemic, but puffy-looking face, and the dejaded look attract attention. Supposing that no relapses occur, the patient rarely recovers perfectly without suffering from rheumatism or some form of neuralgia." The cause of the disease Marston guessed to be filth and poor sanitation.

However, there was no clear general recognition of the disease until Bruce (Ref. 2) isolated the causal organism, as is shown by the confusion displayed in contemporary accounts (S. F. Duffey: On rheumatic orchitis as a sequel to fever, Dublin J. Med. Sc. *53:* 97, 1872; W. C. McLean: On "Malta Fever";

*The book by William Burnett (*A Practical Account of the Mediterranean Fever, as it appeared in the ships and hospitals of His Majesty's Fleet on that station: with cases and dissections*, London, 1816, J. Callow) is mentioned as giving an early account of Malta fever but one searches through it in vain for anything that can be recognized as the disease in question.

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with a suggestion, Brit. M. J. *2:* 224, 1875; O. G. Wood: Malta fever, Edinburgh M. J. *22:* 40, 1876; J. Lane Notter: On Malta fever, ibid., p. 289).

2. Bruce, David: Note on the Discovery of a Micro-organism in Malta Fever, Practitioner *38:* 161, 1887.

Bruce, working in the Army at the Station Hospital at Valletta, Malta, begins his paper as follows: "This fever . . . has a wide distribution in the Mediterranean. It is identical with the Rock fever of Gibraltar, the Neapolitan fever of Naples, the Country fever of Constantinople, and the New fever of Crete. . . . On further investigation I have no doubt this list could be much enlarged. . . ." Although a good deal has been written on the clinical aspects of this fever, "There is, as far as I am aware, no notice regarding the presence of micro-organisms in the organs of fatal cases."

Bruce next sketches the clinical features: "It is a disease of long duration, ninety-one cases . . . having an average stay in hospital of 85.5 days. The fever which often runs high, is continued, remittent and intermittent in type. . . . An undulatory type of curve is frequently observed, the undulations being separated by a period of apyrexia. . . . Sometimes these undulations persist for a long time: in one case I observed two well-marked waves between the 120th and 160th days of the disease." Bruce also emphasizes enlarged spleen, sweats, constipation, bronchitis, pains, swelling of joints, and orchitis. "The mortality is as a rule exceedingly small."

Five fatal cases were examined for micro-organisms, the first by means of stained sections, the remaining four by inoculation into tubes containing agar-agar nutrient jelly. In the first case sections of spleen stained by Gram's method and also with methylene blue showed enormous numbers of single micrococci scattered through the tissues. Bruce next inoculated blood from severe cases, obtained by puncturing the finger tip, into tubes of agar; they remained sterile except for two which were obviously contaminated. Bits of spleen were also inoculated into the tubes. Growth was slow, but it appeared in all the tubes placed in the incubator at 37° C. after a period of 68 hours. "The growth appeared at first as minute pearly-white spots scattered around the point of puncture. Small round colonies could be seen along the needle track . . . examined under a high power, innumerable small micrococci are seen." Similar findings were obtained in three other fatal cases. "From a consideration of the above facts I think it will appear to be sufficiently proved: (a) that there exists in the spleen of cases of Malta fever a definite micro-organism; and (b) that this micro-organism can be cultivated outside of the human body. . . . I have already cultivated four successive generations. It remains now to be seen what effect, if any, this micro-organism has on healthy animals; . . . where it is to be found; how it gains entrance to its human host; and many other points." Curiously enough, Bruce does not state whether the organism was gram positive or negative. He does emphasize the absence of intestinal lesions, thus eliminating confusion with "enteric" fever.

In a second paper (The Micrococcus of Malta Fever, ibid. *40:* 241, 1888), Bruce obtained the same organism from another fatal case and describes it more

in detail. "It is oval in form and measures from .0008 millimetres to .001 millimetres. . . . In sections they are seen to be scattered singly or in pairs throughout the substance of the tissue, and never occur in masses." "One fact to be noted is the rapidity with which the micrococci became wholly unstained by the addition of absolute alcohol." The organisms showed no sign of growth at a temperature below 22° C. Bruce gives a frequency curve of case incidence; most cases occurred May to August, but some were encountered even in winter. Bruce injected some culture into a monkey's arm; after a severe febrile illness the animal died and the organism was recovered from spleen and liver. Small animals on the whole gave negative or doubtful results on inoculation.

3. Bruce, David: Observations on Malta Fever, Brit. M. J. *1:* 1101, 1889.

Bruce, no longer in Malta, but now Assistant Professor of Pathology at the Royal Victoria Hospital, Netley, writes a masterful systematic article on Malta fever. He begins with "Definition. An endemic disease of long duration, characterized by fever, continuous, remittent and intermittent in type, in most cases enlarged spleen, profuse perspiration, sudamina, constipation, relapses almost invariably, accompanied by pains of a rheumatic or neuralgic character, sometimes swelling of joints or orchitis, ending almost always in complete recovery; in fatal cases enlargement and softening of spleen, congestion of the duodenum and upper part of jejunum, no swelling or ulceration of Peyer's glands, and the constant occurrence in various organs of a species of micrococcus." These various features are next analyzed in detail; the prevalent view that this, like many other fevers, was due to sewage, "bad air," or bad smells is discussed. Bruce points out that young adults are most frequently affected; that Malta fever alternates with enteric fever, from which and from malaria it must be differentiated; that whether or not one attack conveys immunity is uncertain. The details of symptoms are analyzed in brilliant fashion as the differential diagnosis is discussed. As to pathologic changes Bruce describes as the prinicipal lesion proliferation of endothelial cells in lymph nodes, spleen and other organs, together with congestion, cloudy swelling and in certain situations infiltration of small round cells. The lesions of typhoid and malaria are definitely absent. He concludes: "1. Malta fever is a specific disease. . . . 2. It is caused by the entrance into the system of a minute parasite. 3. No drug at present known has any power of modifying the action of the bacteria in the system. 4. Treatment is to be principally directed to keeping up the patient's strength by fluid, easily digested food, and, when required, by stimulants, and by attention to ordinary hygienic principles. Removal of the patient from the infective area does not cut short the course of the fever."

Bruce knew nothing of the chronic low-grade forms of infection; he thought of the disease as analogous to typhoid. In these papers there is also no mention of goats or any implication that they are concerned with the disease. The mode of entry of the organism was a complete mystery.

In still another paper (Notes on Mediterranean or Malta Fever. I. Its Bacteriology, Brit. M. J. *2:* 58, 1893) Bruce added still more observations, all

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confirmatory. He produced the disease in several monkeys from which he again recovered the organism which he now calls *Micrococcus melitensis.** A beautiful undulating temperature chart from Monkey VI is reproduced, extending over a period of 98 days. The bacteriologic features are redescribed in detail and Bruce now states that the organism is gram negative.

4. Hughes, Louis: Investigations Into the Etiology of Mediterranean Fevers, Lancet *2:* 1265, 1892.

A. G. P. Gipps (On Malta Fever, Trans. Epidem. Soc. (Lond.) n.s., *9:* 76, 1891) isolated an organism similar to that of Bruce from two cases of Malta fever but Hughes' work, also done in Malta, was much more extensive. He again describes the disease: "Clinically it has a peculiarly irregular temperature curve, consisting of intermittent waves of pyrexia of a distinctly remittent type, each wave lasting from one to three weeks, with generally an apyrexial interval of two or three days. . . . This pyrexial condition is usually very chronic, lasting even six months or more, and is not markedly affected by quinine or arsenic. It is usually accompanied in obstinate constipation, progressive anemia and debility, and is followed, in a large number of cases, by very chronic neuralgic and rheumatic complications from which the patient may not recover for perhaps two years. The death rate is very low; but as the average stay in hospital is 70 to 90 days the expense incurred by the State . . . has reached an enormous sum." Hughes recovered the organism from the spleens of five fatal cases; he carried it through six generations of pure culture. In two cases it was demonstrable microscopically in fresh splenic substance. The organism was not found in other disorders such as enteric fever. Hughes produced the disease in series in monkeys. He gives a detailed description of the organism and its cultural characteristics. He emphasized the slow-growing delicate character of its growth on the available media. Hughes concluded that the presence of the organism was connected with human excrement but he also believed "that the poison of this fever, when infecting the human body, is aerial in nature . . . and that in most cases it enters the human frame by way of the air passages." No mention is made of goats.

It is of interest that both Bruce and Hughes were so imbued with the current theories of miasms that they were reluctant to give up the idea of airborne infection even though they had produced Malta fever in monkeys by subcutaneous injection.

Both Bruce (Sur une nouvelle forme de fièvre rencontré sur les bords de la Méditerranée, Ann. Inst. Pasteur *7:* 289, 1893) and Hughes (Sur une forme de fièvre fréquente sur les côtes de la Méditerranée, ibid., p. 628) wrote systematic articles on the disease in 1893, using mainly their old material. Hughes concludes his paper in rather confused fashion: "It appears to be a contagious fever of a mobile type (*d'un type mobile*) characterized by an indefinite duration, and

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*"This morn we came near Malta, or, as 'twas called formerly Melita, from the abundance of honey they have there, gathered by the bees from the aniseeds and flowers thereof, which grow on this island abundantly"—The Diary of Henry Teonge, chaplain on board H.M.'s Ships Assistance, British and Royal Oak 1675-1679, New York, 1927, Harper & Bros.

an irregular course caused by a poisoning of the blood of fecal origin and capable of assuming an aerial organized form." Bruce on the other hand is more clear. "I believe I have shown that the *Micrococcus melitensis* is the cause of Mediterranean fever and that this is an absolutely specific disease distinct from typhoid and malaria. As to the important question of the mode of entry of the parasite into man whether by air, water or food one does not know yet, and the difficulty in growing the organism is an obstacle in answering this question."

5. Hughes, M. Louis: Undulant (Malta) Fever, Lancet *2:* 238, 1896.

Hughes first gives an immense list of the names which have been applied to the disease, and, after criticizing them, suggests the designation "undulant fever." "It has occurred to me that the term "Undulant Fever" by referring to the peculiar pyrexial curve so characteristic of the disease, might prove a serviceable name. The name appeals forcibly to the clinical observer, who standing in a ward surrounded by cases of this fever (as anyone may do in summer in any of the military hospitals of Malta) gazes at the temperature charts on the walls and notices the way in which the recorded pyrexial curves undulate across the paper in waves of varying degree."

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6. Hughes, M. Louis: Mediterranean, Malta or Undulant Fever, London, 1897, Macmillan & Co.

This book is a landmark in the history of the subject as Hughes summarized in authoritative fashion all that was known to date about the disease. "When the writer arrived in Malta towards the end of the year 1890, for a six year tour of service in that place, he found that his medical work would chiefly consist, during the greater part of the year, of treating a fever about which no two medical officers appeared to agree, respecting its cause, treatment, or even name. Some even doubted its specific nature, calling it a variety of enteric or malarial fever, and until the writer had been present at a post-mortem examination on a fatal case, he was himself prejudiced in favour of all serious cases being of an enteric [typhoid] nature. The fallacy of this theory soon became apparent, and extended clinical and pathological experience showed how much there was to learn, and how little to guide anyone, in the study of this important fever." Hughes himself acquired Malta fever and learned first hand about it. (Preface.) He gives the following definition of the disease on which he elaborates at length: "An endemic pyrexial disease, occasionally prevailing as an epidemic, having a long and indefinite duration, an irregular course with an almost invariable tendency to undulatory pyrexial relapses. It is usually characterized by constipation, profuse perspirations, and accompanied or followed by symptoms of a neuralgic character. Often accompanied by swelling and effusion of the joints and other rheumatoid symptoms. After death, the spleen is found to be enlarged and often softened, many of the organs congested, but Peyer's glands neither enlarged nor ulcerated, nor is ulceration present in other parts of the small intestine. There is a constant occurrence in certain tissues of a definite species of micro-organism" (p. 1). He insists that undulant fever is a specific disease to be clearly distinguished from typhoid fever and malaria; he discusses

the differential diagnosis in detail. He gives arguments in favor of the name he has suggested—undulant fever. Then comes an historical sketch of the disease of the greatest value followed by an invaluable bibliography through 1897, giving many references not to be found anywhere else. The next chapter deals with a description of the organism and the results of animal inoculation. As to predisposing causes Hughes went wrong like all before him, and vaguely blamed the disease on lack of sanitation, which certainly was outstanding in Malta at the time and is graphically described. Goats are not mentioned anywhere in the book. While the disease occurred through the year, most cases occurred in July, August, and September. Apparently one attack confers immunity. Hughes distinguishes malignant cases—very severe although rarely fatal, the undulatory type—"finally the patient is reduced to an emaciated, anaemic, and bed-ridden condition"—, an intermittent type and irregular and mixed types. There is a brilliant section on symptoms in detail—with illustrative temperature curves—in which every phase of the clinical features is analyzed. The over-all mortality was about 2 per cent. The gross morbid changes at autopsy are not very striking; the spleen is invariably enlarged and congested. Microscopically the appearances "are not in any way specially characteristic of undulant fever, but rather those of severe and prolonged pyrexia acting on the tissues of the body." Neither Hughes nor Bruce apparently found the specific lesion described later (Refs. 24, 30). As to treatment, "There is no drug of a specific nature at present known which will cut short an attack of the fever by its action on the virus as does quinine in ague, and mercury in syphilis."

7. Wright, A. E., and Smith, F.: On the Application of the Serum Test to the Differential Diagnosis of Typhoid and Malta Fever, Lancet *1:* 656, 1897.

Wright, who was an early pioneer in serodiagnosis of infections, describes the technique of his method. Serum from the patient was mixed with young cultures of various bacteria in capillary tubes. A positive test was indicated by macroscopic clumping. Wright was able by means of this test to differentiate clinically doubtful cases of Malta fever and typhoid fever. In another paper (A. E. Wright and D. Semple: On the Employment of Dead Bacteria in the Serum Diagnosis of Typhoid and Malta Fever, Brit. M. J. *1:* 1214, 1897), the use of dead cultures was introduced and found to give just as definite results as live organisms. Wright and Semple spoke of the advantages of this method to the general practitioner. "It will obviously be possible for every medical man to obtain a supply of capsules of dead typhoid and Malta fever bacteria for serum diagnosis from a central laboratory. He will be able to carry about these cultures without risk. . . ."

8. Musser, J. H., and Sailer, Joseph: A Case of Malta Fever, Phila. M. J. *2:* 1408, 1898.

The writers report a typical case of "Malta fever" in an army officer who probably contracted the disease in Puerto Rico. A characteristic chart of prolonged undulating fever is shown and the patient's serum agglutinated a culture of Bruce's organism in a dilution of about 1:50. In "Further Notes on a Case

of Malta Fever; A Study in Serum Diagnosis," ibid. *4:* 89, 1899, they give a follow up report on this patient, whose fever dragged along and whose serum repeatedly agglutinated *Micrococcus melitensis*, but gave no Widal reaction for typhoid.

This is claimed to be the first case reported in the Western Hemisphere.* Charles F. Craig (The Symptomatology and Diagnosis of Malta Fever With the Report of Additional Cases, Internat. Clin. *4:* 89, 15th Series, 1906) described instances from the Army, including one of a nurse who had never been out of the country, apparently the first recorded indigenous case. Her serum agglutinated the organism in a dilution of 1:250. Craig also refers to chronic cases. "In many cases of Malta fever, however, after the initial attack, a chronic infection results and is characterized by symptoms so slight as to be almost unrecognizable unless watched for and understood." He pointed out that this form of the disease is often confused with chronic arthritis and muscular rheumatism and reports examples. Malaria, typhoid fever, tuberculosis, pneumonia, septicemia, relapsing fever, Hodgkin's disease, and articular rheumatism are to be considered in the differential diagnosis. He also emphasized the lack of pathognomonic symptoms, postulated a wide unrecognized distribution of the disease and the importance of applying the "serum-test" in all undetermined cases of fever in all regions.

Thus Craig definitely widened the concept of the disease from that of the early writers (see also Ref. 17).

9. Bang, B.: Die Aetiologie des seuchenhaften ("infectiösen") Vervorfens, Ztschr. f. Thiermed. *1:* 241, 1897.

Abortion of cattle had long been considered contagious. Penberthy (Enzootic Abortion, J. Comp. Path. & Therap. *8:* 100, 1895) quotes a statement in the *Complete Farmer* for 1807 as follows: "It is considered certainly contagious and when it happens the abortion should be immediately buried and the cow kept as widely apart as possible from the herd." As the bacteriologic era developed, it was inevitable that an infectious agent should be sought. Nocard, for example, (Récherches sur l'avortement epizootique des Vaches, Rec. de méd. vet. *3:* 669, 1886) made cultures from the puriform material laid down between the uterus and ovum and isolated two types of bacteria, micrococci and short thick bacilli. Although he was not able to grow them in pure culture, it is highly probable that the "micrococci" were identical with *B. abortus*. Bang was able to obtain the generative organs fresh from a cow in which abortion was threatened. Cultures were made within six hours of death. When the uterus was opened under aseptic conditions, "We saw between the mucosa and the egg an abundant, non-odorous exudate . . . the examination of cover glass preparations of this material stained with methylene blue (Loeffler) immediately disclosed the presence of very small bacteria apparently in pure culture . . . infectious abortion

*The cases of J. M. Da Costa (Protracted Continued Fever, Am. J. M. Sc. *3:* 629, 1896), sometimes mentioned in the literature as being instances of brucellosis, are too indefinite to allow any conclusions. Such cases at the time were often called typhoid-malaria, the designation used in the first run of the Surgeon General's Catalogue.

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is to be considered as the consequence of a specific uterine catarrh caused by a special bacterium." Bang was able to grow the organism in pure culture in deep tubes of serum gelatine agar in which colonies appeared in a definite zone about 0.5 cm. under the surface and 1 to 1.5 cm. thick. No colonies grew above or below this zone, which indicated that the organism was sensitive to oxygen tension. The colonies were small and round and consisted of small bacilli of the same appearance as those found in the uterine exudate. Further cultural characteristics are given. Bang soon obtained material from 21 cases of contagious abortion and the "*Abortusbacilli*" were found in practically all. In two experiments in which a pure culture of the bacillus was introduced into the vagina of the cow, abortion followed. "By these two observations we have brought full proof that the organisms discovered by us are the cause of epidemic abortion." "We have had no opportunity to experiment with goats," but "a colleague saw a goat abort living in a stable where cows had previously aborted. This makes it highly likely that our bacillus is also infectious for goats." Here then is the first hint of a relation between Malta fever of goats and contagious abortion of cattle.

Bang's work was soon confirmed by Hugo Preisz (Der Bacillus des seuchenhaften Vervorfens, Centralbl. f. Bakt., 1 Abt. Orig., *33:* 190, 1903) and subsequently by many other workers.

10. Birt, C., and Lamb, G: Mediterranean or Malta Fever, Lancet *2:* 701, 1899.

Final direct proof of the causal role of *M. melitensis* in Malta fever was brought by laboratory infections, two of which were reported by these authors. In one case a man accidentally scratched himself with the needle of a syringe with which he had just injected living growth into a horse. Fifteen days later he went through a typical attack of Malta fever. In a second case a man injected a small amount of agar culture into his arm. Sixteen days later symptoms set in and he pursued a characteristic course. K. F. Meyer and B. Eddie (Laboratory Infections due to Brucella, J. Infect. Dis. *68:* 24, 1941) later reported and analyzed "74 histories of brucellosis observed among bacteriologists, pathologists and other workers who in the course of their duties were exposed to Brucella in the laboratories of the United States." They adduced evidence that "injections with dead vaccines fail to prevent laboratory infections."

11. Leishman, W. B.: Some Experiments in Connection With "Stimulins," Tr. Path. Soc. London *56:* 344, 1905.

Leishman, working in the early days of studies on phagocytosis and opsonins ("stimulins") showed that ingestion of *M. melitensis* by leukocytes was tremendously increased by adding a little Malta fever convalescent serum to the mixture. The average number of germs phagocyted by each polynuclear was increased, for example, from 17.6 to 70. I. F. Huddleson, H. W. Johnson, and E. E. Hamann (A Study of the Opsono-cytophagic Power of the Blood and Allergic Skin Reaction in Brucella Infection and Immunity in Man, Am. J. Pub. Health *23:* 917, 1933) later elaborated and laid stress on this test, along with a skin

test, as an indication of infection with Brucella. "Infection in an individual is indicated by a positive allergic skin test obtained with Brucella nucleo-protein in conjunction with negative or low opsono-cytophagic activity of the whole citrated blood for Brucella." The value of this test has been variously judged by others (Ref. 44).

12. Reports of the Commission appointed by the Admiralty, the War Office and the Civil Government of Malta, for the investigation of Mediterranean Fever, under the supervision of an Advisory Committee of the Royal Society, Parts I-VII. London, 1905-1907, Harrison & Sons.

"The Mediterranean Fever Commission had its origin in a letter from Mr. Secretary Lyttleton, dated January 25, 1904, addressed to the Royal Society, in which he states that his attention has recently been called to the prevalence of Mediterranean fever in Malta among the Naval and Military forces, as well as the civil population.

"It accordingly appeared to him to be desirable that the investigation of this fever should be taken in hand, and he addressed a despatch to the Governor of Malta proposing the appointment of a joint Commission representing the Army, the Navy and the Civil Government."

The Royal Society nominated a committee to direct the investigations which appeared in seven parts over a period of three years. Every phase of the subject was studied—bacteriology, epidemiology, relation of the disease to goats, transmission to animals, and clinical features. In the final section practical recommendations for controlling Malta fever are made. The Commission did monumental work and really "skimmed the cream" for all time in the study of the disease.

In subsequent sections we shall mention some of the most important individual studies; they will be listed under the heading "British Commission."

13. Horrocks, W. H.: Further Studies on the Saprophytic Existence of Micrococcus melitensis, British Commission, Part I, p. 14, 1905.

The author concludes "1. The M. melitensis retains its vitality in sterilized tap water for 37 days. 2. In a Maltese soil, allowed to dry naturally, the M. melitensis survives 43 days. . . . 3. The M. melitensis survives for 72 days in a damp soil. 4. Exposure to the sun for a few hours kills the M. melitensis. 5. The M. melitensis survives for 25 days in sterilized sea-water."

14. Horrocks, W. H.: On the Recovery of the Micrococcus melitensis From the Urine, Faeces, and Sweat of Patients Suffering from Mediterranean Fever, British Commission, Part I, p. 21, 1905.

Horrocks isolated the organism from the urines of many patients from the fifteenth to the eighty-second day of disease; he was unable to isolate it from feces or sweat. J. Crawford Kennedy (On the Recovery of Micrococcus melitensis From the Urine of Mediterranean Fever Patients, ibid., Part III, p. 56, 1905) recovered the organism from 186 of 1,974 samples of urine examined. He found that excretion would appear to be of two kinds: (1) an enormous sudden

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gush or (2) a long-continued excretion of small quantities. Bacteremia continued in some cases after the patients were discharged as clinically well.

15. Gilmour, R. T.: Description of a Method of Cultivating the Micrococcus melitensis From Small Quantities of Peripheral Blood and Inoculation Experiments With the Micro-organisms Isolated, British Commission, Part I, p. 73, 1905.

Gilmour drew blood by venipuncture and succeeded in isolating *M. melitensis* in broth culture. It is of interest that preparation for the procedure consisted of shaving the arm, scrubbing with brush and carbolic soap, with sterile nail brush and water for 20 minutes, swabbing with ether for 10 minutes, and finally scrubbing with perchloride of mercury for ¼ hour. "A sterile dressing should then be applied, soaked in the same disinfectant, until the time of the operation [the venipuncture], about 24 hours afterwards." E. A. Shaw (Interim Report of Experimental Work, etc., British Commission, Part I, p. 95, 1905) summarized the work of the Commission to date and points out with reference to blood culture that the organism exists in the circulation "in relatively very small amount," that it may be isolated at any stage of the disease, as early as the 7th day, as late as the 98th, and even after the temperature has been normal for several days, as in Keefer's case (Ref. 31), and that there was no regular relation between the number of organisms in the blood and its agglutinating power. In a still later paper, Shaw (On the Quantitative Bacteriological Examination of the Blood of 103 Mediterranean Fever Patients, British Commission, Part III, p. 5, 1905) reported isolation of the organism in about two-thirds of the patients, "M. melitensis exists in the blood in relatively small amount, not having been found in association with a less quantity of blood than 4 cu.mm., and that only in two cases out of 103."

16. Horrocks, W. H.: Preliminary Note on Goats as a Means of Propagation of Mediterranean Fever, Proc. Roy. Soc., London, *76:* 378, 1905.

Horrocks wished to ascertain, by experimental inoculation, whether goats could be infected by *M. melitensis.* Preliminary examination of the animals showed, however, that their serum agglutinated the organism in dilutions up to 1:300, and that cultures of milk even when the goat appeared well often yielded *M. melitensis.* Horrocks concluded: "The results obtained show that some of the goats in every herd examined are suffering from Mediterranean fever. The M. melitensis is exuded in the milk in enormous numbers when the disease has been present sufficiently long. . . ." He also isolated the organism from the urine of goats "when the disease has existed for some time."

With Horrocks in this work was associated Dr. T. Zammit who actually carried out the first agglutination tests with the sera of six goats (A Preliminary Note on the Examination of the Blood of Goats Suffering From Mediterranean Fever, British Commission, Part III, p. 83, 1905). This was the first proof that goats were of importance in the transmission of Malta fever. Horrocks, with J. C. Kennedy (Goats as a Means of Propagation of Mediterranean Fever, British Commission, Part IV, p. 37, 1906) later elaborated his early studies. He found

that 41 per cent of the goats in Malta were infected, judged by the serum reaction, and that 10 per cent of the goats supplying milk appeared to excrete *M. melitensis*, often with no change in the physical characteristics of the milk and without the animal exhibiting signs of ill health. Excretion was often intermittent. Monkeys and goats were infected by feeding cultures or by feeding infected milk, with an incubation period of three to four weeks. Goats also became infected by feeding on dust polluted with urine from patients. Finally Horrocks found that pasteurization (68° C. for 10 minutes) destroys the *M. melitensis* in infected goats' milk.

17. Shaw, E. A.: The Ambulatory Type of Case in Mediterranean or Malta Fever, British Commission, Part IV, p. 8, 1906.

Shaw examined the blood of 525 dockyard workers, all apparently healthy. Among these a markedly positive agglutination reaction was given by the blood serum in 22 cases. On taking the temperatures, several had slight elevations of over 99 degrees. From three of these cases *M. melitensis* was recovered from both blood and urine; from one it was obtained from the blood only and from six from the urine only. The author concludes that the existence of ambulatory cases, previously uncertain, is now proved. (See also Craig, Ref. 8.)

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Observations of this sort have been repeatedly made through the years, as for example by Parker Dooley (Undulant Fever, an Epidemic of Subclinical Infection With Brucella, Arch. Int. Med. *50:* 373, 1932), who found that in a group of 263 persons using infected raw milk, 41 per cent were found to have serum agglutinins against *Brucella abortus*, and two had clinical undulant fever.

This phase of the subject has recently been subjected to penetrating analysis by W. W. Spink (What Is Chronic Brucellosis? Ann. Int. Med. *35:* 358, 1951). He discusses the vague entity often diagnosed chronic brucellosis and sets up criteria which justify a positive diagnosis.

18. Shaw, E. A.: Mediterranean Fever in Goats, Cows and Other Animals, British Commission, Part IV, p. 16, 1906.

Shaw infected goats experimentally and also studied the incidence of natural infection. Of 96 goats in full milk, 30 were found to have sera which agglutinated *M. melitensis*. Organisms were recovered from the milk in 9 of these and their infectivity was demonstrated on a monkey. Shaw thought the most likely route of infection was via the gastrointestinal tract. It is of great interest that he found 10 of 33 *cows* infected; *M. melitensis* was recovered from the milk of two of them. No relation was sensed, however, between these findings and those of Bang (Ref. 9).

19. Kennedy, T. Crawford: Bacteriological Examination of Cases of Mediterranean Fever, British Commission, Part IV, p. 92, 1906.

In post-mortem material *M. melitensis* was frequently recovered from spleen, liver, kidney, lymph nodes, bone marrow, and bile, but never from intestines, salivary glands, tonsils, pleural or cerebrospinal fluid.

20. Davies, A. M.: Report on the Prevalence of Mediterranean Fever Amongst British Troops in Malta, 1905, British Commission, Part IV, p. 105, 1906.

It is of interest that at the end of this elaborate study the writer concludes that water and milk have nothing to do with transmission, but that infection occurs most likely "by direct or semi-direct contagion or through the agency of mosquitos."

21. Eyre, J. W. H., McNaught, J. G., Kennedy, J. C., and Zammit, T.: Report Upon the Bacteriological and Experimental Investigations During the Summer of 1906, British Commission, Part VI, p. 3, 1907.

This report contains, among other interesting material, an account of the famous incident of the outbreak of Mediterranean fever on board the S. S. *Joshua Nicholson*, which was transporting 61 milch goats from Malta to Antwerp where they were transferred to the S.S. *St. Andrew* bound for New York. During the voyage the personnel of the ship drank largely of goats' milk and a considerable number acquired Malta fever. Thus there was carried out an "unpremeditated experiment" in transmission of the disease from goat to man. A more complete history of this outbreak is given by F. H. A. Clayton (British Commission, Part VII, p. 107, 1907).

Among the conclusions of this report were the following. The most common method of acquiring the disease is by the ingestion of infected articles of food—mainly milk. The next common path of infection is by subcutaneous inoculation (see also Ref. 32) during the handling of contaminated material—usually milk. *M. melitensis* is not destroyed during the processes incident upon the manufacture of the ordinary ice creams, or of the native cheeses, and it may be present in the retail articles living and unaltered in virulence.

As a result of these studies, the writers drew up "Recommendations as to preventive measures in connection with Mediterranean fever in Malta" of which the main points were the control of infected animals and the elimination of infection in food stuffs.

22. Ferenbaugh, Thomas L.: Endemic Mediterranean Fever (Malta Fever) in Southwest Texas, J.A.M.A. *57:* 730, 1911.

Ferenbaugh first suspected that "goat fever" which occurred in young men working in a "goat camp" in the Pecos River country was really Malta fever. He reported four patients with indeterminate prolonged fever whose sera all gave positive agglutination tests with *M. melitensis*. In a second paper with Gentry (E. R. Gentry and T. L. Ferenbaugh: Endemic Malta [Mediterranean] Fever in Texas With the Isolation of the Micrococcus melitensis from Two Patients, J.A.M.A. *57:* 889, 1911) he isolated the organism in broth cultures from two more patients. In a third paper, Gentry and Ferenbaugh (Endemic Malta [Mediterranean] Fever in Texas, ibid., p. 1045) made an epidemiologic study in which they demonstrated infection by means of agglutination tests in 34 per cent of the goats examined. "All cases of Malta fever found have occurred in territory devoted to goat-raising and all patients either gave a history of drinking unboiled goats milk or were actively connected with the goat-raising industry."

Finally, in a fourth paper (Malta Fever in Texas, ibid., p. 1127), they reported more extensive observations on infection among the bands of goats of which there were approximately 175,000, raised for the mohair which they produce. They suggested that infection arose from dust as well as milk drinking. These studies were of great importance because they demonstrated endemic infection in a goat-raising area in the United States quite analogous to the situation in Malta.

23. Schroeder, E. C., and Cotton, W. E.: II. The Bacillus of Infectious Abortion Found in Milk. Twenty-Eighth Annual Report of the Bureau of Animal Industry, U.S. Dept. of Agriculture, Washington, 1911, p. 139.

During routine tests for tubercle bacilli in milk by means of guinea-pig inoculation, curious lesions (see Ref. 24) resembling tuberculosis but lacking acid-fast bacilli were encountered in some animals. The disease was transmissible from guinea pig to guinea pig. Milk from perfectly healthy cows, tuberculin negative, sometimes produced these lesions. A small organism, identified as *Bacillus abortus*, was found in the milk which caused the disease resembling tuberculosis. There is a detailed description and good pictures of the lesions in the guinea pig which correspond to those described by Smith and Fabyan (Ref. 24). The striking thing in this study was the frequent occurrence of *B. abortus* in the milk of perfectly healthy cows. The writers did not definitely link these milk-borne bacilli to any human disease, but they did think that "the germ forms another link in the long chain of facts that point unmistakably to the proper pasteurization of all milk . . . as a measure essentially necessary for the protection of public health." A few years later E. C. Fleischner and K. F. Meyer (Observations on the Presence of the Bacillus abortus bovinis in Certified Milk, Am. J. Dis. Child. *14:* 157, 1917) carefully reviewed the whole subject and added observations of their own from which they concluded: "B. abortus is, for practical purposes, always present in the certified milk produced in the San Francisco Bay regions."

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24. Smith, Theobald, and Fabyan, Marshall: Ueber die pathogene Wirkung des Bacillus abortus Bang, Centralbl. f. Bact., 1 Abt. orig., *61:* 549, 1912.

After the appearance of the Report of the British Commission, it was assumed that all Malta fever resulted from drinking goats' milk or other contact with goats. Until the work of Smith and Fabyan, infection with *B. abortus* remained a strictly veterinary problem. No relation between the two in the causation of disease was suspected. Smith and Fabyan were able to produce with material from contagious abortion a chronic disease in guinea pigs featured by enlarged and engorged spleen, enlarged lymph nodes, and small nodules in the liver. The disease was passed in series through guinea pigs, and *B. abortus* was isolated in pure culture from the lesions which were reproduced by it. The disease ran as long as eleven months without very drastic external appearances. Sometimes there were overt lesions of bones and joints. Smith and Fabyan found microscopically "a chronic inflammatory process closely resembling tuberculosis." There were foci of epithelial cells and lymphoid cells occasionally with necrotic centers. The details must be read in the original communication.

Bacilli were found especially in spleen, but also in lymph nodes, bone marrow, liver, kidney, and lung, and were grown from the lesions. Smith and Fabyan concluded first that contagious abortion was caused in America as in Europe by *B. abortus* Bang. Second, they suggested that the overt lesions of contagious abortion were not always primary but were secondary to slow general infection of the sort described in guinea pigs. "That the 'Abortbacillus' appears in milk is very probable." Conclusions: (1) B. abortus Bang is most probably the only cause of contagious abortion. (2) B. abortus produces in guinea pigs a peculiar generalized disease which rarely leads to death. It resembles tuberculosis, and is characterized by chronic interstitial new growths, which for the most part consist of epithelial and lymphoid cells. (3) B. abortus can be present in milk and it is therefor indicated to investigate whether it has any causal relationship with any chronic disease of man."

M. Fabyan (A Contribution to the Pathogenesis of B. abortus Bang—II. J. Med. Research *26:* 441, 1912) a little later wrote up much the same material in English. He described in great detail the pathology of the disease produced in guinea pigs.

25. Nègre, L., et Raynaud, M.: Melitensis et paramelitensis, Compt. rend. Soc. de biol. *72:* 791, 1912.

The authors had already shown (Sur l'agglutination du "Micrococcus melitensis" par les sérums humains, ibid. *70:* 472, 1911) that *Micrococcus melitensis* was agglutinated frequently not only by sera from patients with Malta fever but by many "normal" sera as well. The present study concerns a strain of *M. melitensis*, with all the typical cultural characteristics, which agglutinated only feebly with convalescent Malta fever serum, whereas five other strains were agglutinated in titers of 1 to 1,000 to 1 to 5,000. An immune serum, however, prepared from this strain failed entirely to agglutinate the other five strains, whereas it agglutinated the homologous strain in a titer of 1:500. Thus they had separated an immunologically different strain of *M. melitensis* which they designated paramelitensis by analogy to parameningococci and paradysentery bacilli. This work was later extended (Identification des Paramelitenses, par l'épreuve de la saturation des agglutinins, ibid., p. 1052) by agglutination and absorption tests.

26. Larson, W. P., and Sedgwick, J. P.: The Complement Fixation Reaction of the Blood of Children and Infants, Using the Bacillus abortus as Antigen, Am. J. Dis. Child. *6:* 326, 1913.

From the work of Cotton and Schroeder (Ref. 23) the writers knew that 10 per cent of market milk contains *B. abortus*, and also that animals may be infected per os. They wondered therefore whether humans were ever infected; and they examined the blood of 425 children by complement fixation, using *B. abortus* as antigen. Of these 425 they found 73 positive. The antibodies could also be absorbed by suspensions of the bacilli. These investigators definitely raised the question of human infection with *B. abortus*, but they went no further and made no suggestion of the occurrence of undulant fever in man as a result of infection with it.

27. Report of the Chief of the Bureau of Animal Industry. Annual Reports of the Department of Agriculture for the Year Ended June 30, 1914. Washington, Government Printing Office, 1914, p. 86.

The report includes reference to premature hairless pigs which were sent in to the Department for examination. "Cultures made from liver, stomach contents and kidneys revealed an organism resembling Bacillus abortus in cultural and morphological characteristics. These cultures when used as antigens in both agglutination and complement-fixation tests gave the same results with two known negative, two known positive and with unknown bovine sera, as were obtained with an antigen prepared from B. abortus of Bang from bovine origin." This seems to be the first report of a porcine strain. Whereas the finding is often attributed in the literature to J. Traum (see, for example, H. J. Harris: Brucellosis, ed. 2, New York, 1950, Paul B. Hoeber, p. 9), his name is actually not mentioned in the report which emanated from the Pathological Division under the direction of Dr. John R. Mohler. Actually E. S. Good and W. V. Smith (Bacillus abortus [Bang] as an Etiological Factor in Infectious Abortion of Swine, J. Bact. *1:* 415, 1916) seem to have first isolated from the afterbirth of an aborting sow and from numerous other tissues organisms which they were unable to distinguish from *B. abortus*.

C. P. Beattie and R. M. Rice (Undulant Fever Due to Brucella of the Porcine Type—Brucella suis, J.A.M.A. *102:* 1670, 1934) report a milk-borne epidemic of thirty cases of undulant fever due to *Brucella suis*. The organism was obtained by blood culture from 6 of 14 patients and from the milk of one cow. Infection with porcine strains seemed especially common in Iowa. A. V. Hardy, C. F. Jordan, and I. H. Borts (Undulant Fever, Further Epidemiological and Clinical Observations in Iowa, J.A.M.A. *107:* 559, 1936) found that 70 per cent of 124 cases were caused by this type. C. F. Jordan and I. Borts (Brucellosis and Infection Caused by Three Species of Brucella, Am. J. Med. *2:* 156, 1947) more recently reviewed the subject.

28. Fleischner, E. C., and Meyer, K. F.: The Bearing of Cutaneous Hypersensitiveness on the Pathogenicity of the Bacillus abortus bovinus, Am. J. Dis. Child. *16:* 268, 1918.

The authors noted the resemblance of the experimental lesions of *B. abortus* in guinea pigs to those of tuberculosis (Ref. 24). Hence they did skin tests with extracts of *B. abortus* and with abortus bacilli. Guinea pigs with lesions invariably gave a positive skin reaction. Guinea pigs which had been injected with dead cultures or in which no disease developed always gave a negative skin test. The authors, therefore, drew analogies to tuberculin testing and concluded that a positive skin test to "abortin" indicated active infection. On the other hand, "In a series of seventy-five infants fed on a high bacillus abortus containing milk, cutaneous hypersensitiveness was not present," and the writers regard this as suggestive evidence that *B. abortus bovinus* is not highly pathogenic for infants.

29. Evans, Alice C.: Further Studies on Bacterium abortus and Related Bacteria. II. A Comparison of Bacterium abortus With Bacterium

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bronchisepticus and With the Organism Which Causes Malta Fever, J. Infect. Dis. *22:* 580, 1918.

Since it had been shown that the Malta fever organism commonly infects goat's milk on the island of Malta and that *B. abortus* commonly infects cow's milk in this country, it occurred to Evans to make a detailed comparison of the two. Using elaborate cultural and immunologic tests she found that "the organism which causes Malta fever is unquestionably a rod form and should be called Bact. melitensis. But melitensis is very closely related to Bact. abortus. The only test which has been found to distinguish these two organisms is the agglutination of Bact. melitensis suspensions in higher dilutions of melitensis serum than will agglutinate suspensions of Bact. abortus. The agglutination tests as they have been used to diagnose infections of Bact. melitensis in goats and human subjects cannot be relied on to distinguish one from the other." This was pioneer work in pointing out the similarity of the bacteria which cause Malta fever and contagious abortion of cattle. Evans continued and elaborated her studies (The Serological Classification of Brucella melitensis From Human, Bovine, Caprine, Porcine and Equine Sources, Pub. Health Rep. *38:* 1948, 1923).

M. L. Fusier and K. F. Meyer confirmed and elaborated Evans' work (Principles in Serological Grouping of B. abortus and B. melitensis. Correlation Between Absorption and Agglutination Tests, J. Infect. Dis. *27:* 185, 1920) and suggested that the "B. abortus and B. melitensis group be given generic rank in the Bacteriaceae family as the genus 'Brucella.'" Meyer also pursued these studies with E. B. Shaw (A Comparison of the Morphological, Cultural and Biochemical Characteristics of Br. abortus and Br. melitensis. Studies on the Genus Brucella, J. Infect. Dis. *27:* 173, 1920).

30. Smith, Theobald: A Characteristic Localization of Bacillus abortus in the Bovine Fetal Membranes, J. Exper. Med. *29:* 451, 1919.

The elucidation of the pathologic histology of Brucella infection was opened by the observations of T. Smith, who found *B. abortus* in the epithelial covering of the chorion. He noted that the more or less specific localization and multiplication of bacteria within cells not having phagocytic functions had been demonstrated in leprosy and syphilis. E. W. Goodpasture and K. Anderson (The Problem of Infection as Presented by Bacterial Invasion of the Chorio-allantoic Membrane of Chick Embryos, Am. J. Path. *13:* 149, 1937) confirmed these findings in chick embryos inoculated with Brucella. They noted that the bacilli enter ectodermal epithelial cells and proliferate there, as they do in chorionic epithelium of the calf. G. F. Buddingh and F. C. Womack (Observations on the Infection of Chick Embryos With Bacterium tularense, Brucella, and Pasteurella pestis, J. Exper. Med. *74:* 213, 1941) described the growth of Brucella in chick embryos more in detail, confirming the findings of Goodpasture and Anderson. They also described involvement of the endothelial cells lining the blood vessels. K. F. Meyer (Observations on the Pathogenesis of Undulant Fever. Essays in Biology, Berkeley and Los Angeles, 1943, University of California Press, p. 439) described the pathologic histology in a laboratory worker who

died within eleven days of an acute septicemia with *Brucella suis*, "First and foremost is the intracytoplasmic multiplication of the bacteria in the epithelium of Bowman's capsule and the convoluted tubules. . . . This selective intracellular parasitism in mesenchyme cells of various organs is doubtless of greatest significance in the pathogenesis of Brucella infections. . . . There is no proof that the brucellas multiply in the blood stream. . . . Their presence in macrophages and polymorphonuclear leukocytes is justly attributed to phagocytosis. . . . Once in the cytoplasma, they find conditions favorable for multiplication and protection against phagocytosis." Meyer gives an interesting and detailed analysis of the problems of pathogenesis of Brucella infection.

Further studies along this line are those reported by W. W. Spink (Pathogenesis of Human Brucellosis With Respect to Prevention and Treatment, Ann. Int. Med. *29:* 238, 1948; Sundberg, R. D., and Spink, W. W.: Histopathology of Lesions in Bone Marrow of Patients Having Active Brucellosis, Blood, Supp. 1., p. 7, 1947; Spink, W. W., Hoffbauer, F. W., Walker, W. W., and Green, R. A.: Histopathology of the Liver in Human Brucellosis, J. Lab. & Clin. Med. *34:* 40, 1949; and M. Ruiz Cestenada: Studies on the Pathogenesis of Brucellosis, Proc. Soc. Exper. Biol. & Med. *64:* 298, 1947).

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31. Keefer, Chester S.: Report of a Case of Malta Fever Originating in Baltimore, Maryland, Bull. Johns Hopkins Hosp. *35:* 6, 1924.

Z. Khaled (A Comparative Study of Bovine Abortion and Undulant Fever From the Bacteriological Point of View, J. Hyg. *20:* 319, 1921) raised the question of "whether or not B. abortus being so closely related to B. melitensis is capable of producing an undulant or other form of fever in man." Without definite proof he reported having seen cases in Egypt "which have never had a chance of ingesting goat's milk and yet suffered from typical melitensis fever confirmed by laboratory diagnosis." Still earlier, C. Kennedy (Preliminary Notes on the Presence of Agglutinins for the Micrococcus melitensis in the Milk and Blood Serum of Cows in London, J. Roy. Army M. Corps *22:* 9, 1914) referred to two cases of undulant fever in people who had never been out of England. It remained for Keefer, however, to report the first case of "a disease in man corresponding to Malta fever due to an organism belonging to the abortus group."* Keefer's patient, a laboratory worker, is of great interest. He ran a typical undulating fever, and between October 19 and January 10 yielded 13 positive blood cultures with one to six colonies per cubic centimeter of Brucella. The infection was probably due to cow's milk and by appropriate serologic tests Keefer showed that the organism was of the abortus type. Thus the Melitensis and abortus types were finally brought together clinically as well as immunologically. Alice Evans was also hot on the trail (Malta Fever. Cattle Suggested

*In regard to Keefer's case, Huddleson (loc. cit., p. 68) says "Duncan [J. T. Duncan, in discussion of "Contagious Abortion and Undulant Fever," Brit. M. J. *1:* 544, 1925] was the first to recognize and report cases of Brucellosis due to Br. abortus." Duncan reports a case in a brief paragraph in which he states conservatively that "the weight of the evidence pointed to B. abortus as the cause of Rhodesian undulant fever in man" but "Experimental proof was still awaited; as also was a really trustworthy test to distinguish B. abortus from B. melitensis." As to Keefer's culture, Huddleson states "Several years later the author had an opportunity to study this culture and it was then found to be Br. suis." At any rate, Keefer reported the first case of what was clinically Malta fever in which a member of the Brucella group other than melitensis was proved to be the cause.

as a Possible Source of Infection, Following a Serological Study of Humans, Pub. Health Rep. *39:* 501, 1924) as a result of comparative study of human sera, but she described no actual patients.

Other cases of "Malta fever" due to *Brucella abortus* were soon reported, such as those of C. M. Carpenter and H. E. Merriam (Undulant Fever From Brucella abortus, J.A.M.A. *87:* 1269, 1926), who described two typical instances in which the organism was isolated from the blood and proved by agglutination absorption tests to be the abortus variety. "Contagious abortion and undulant fever" was also discussed at a meeting of the Royal Society (Brit. M. J. *1:* 554, 1925).

32. Hardy, A. V., Hudson, Margaret G., and Jordan, C. F.: The Skin as a Portal of Entry in Br. melitensis Infections, J. Infect. Dis. *45:* 271, 1929.

The frequency of undulant fever in the employees of a meat packing plant suggested to the writers that Brucella infection through the skin might be a common occurrence. Guinea pigs were readily infected by spreading culture on the shaved or clipped skin. That such infection was not due to organisms which entered via the digestive tract is made clear by the much lower occurrence of infections when culture material was actually fed by mouth. The significance of the skin route seemed to be confirmed by the frequency of infection in workers in the packing house where those who actually killed and cut the animals had the disease much more frequently than those who worked in the offices or elevators, or handled boxes, carried meat, etc.

The importance of infection through the skin had been recognized long before the present work by the British Commission (Ref. 21).

33. Kristensen, Martin, and Holm, Per: Bakteriologische und statistische Untersuchungen über Febris undulans in Dänemark, Centralbl. f. Bakt., 1 Abt., *112:* 281, 1929.

The authors give a critical discussion of the relation of infection with *B. abortus* to abortion in women. They are skeptical about such an infection playing a significant part in human pathology although they allude to the case of a woman who aborted in the seventh month, from whose placenta the abortus bacillus was grown although none was recovered from the organs of the fetus. C. M. Carpenter and R. Boak (Isolation of Brucella abortus From a Human Fetus, J.A.M.A. *96:* 1212, 1931) later isolated *B. abortus* from the placenta and the fetal organs of an early abortion in a woman who did not have undulant fever. They give an exhaustive review of the literature on the finding of abortus in the generative organs of humans and of various animals but leave undecided the case for *B. abortus* playing an important role in human abortion.*

34. Sharp, William B.: Pathology of Undulant Fever, Arch. Path. *18:* 72, 1934.

The morbid anatomy of Brucellosis is comprehensively reviewed with bibliography. The writer points out the scant material in the literature and the

*Dr. Charles E. McLennan, Professor of Obstetrics and Gynecology at Stanford University, tells me that as of today (1955) local infection with *B. abortus* is not considered as significant in human abortion.

paucity of destructive gross lesions. "The most essential item in the general pathologic alteration is a proliferation of cells belonging to the reticulo-endothelial system." H. J. Harris in his book on Brucellosis (loc. cit.) gives a long list of all the lesions which have been described in various organs (p. 91) and then a detailed discussion with references to the literature.

35. Carpenter, Charles M., and Boak, Ruth A.: The Treatment of Human Brucellosis. A Review of Current Therapeutic Methods, Medicine *15:* 103, 1936.

The writers give a comprehensive review, with literature, on the methods of treating brucellosis before the antibiotic era. They point out the difficulty of evaluating any therapeutic measure in a disease which runs such a variable course both as to time and as to severity. They discuss vaccine therapy, serum therapy, therapy with toxic filtrates, therapy with various chemicals such as dyes, arsphenamines, etc., foreign protein therapy, and therapy with induced fever. The conclusion from all of this is, "A successful method for the treatment of brucellosis still awaits development, for as yet no therapeutic agent has been found which has been proved to alter, to a significant degree, the natural course of the disease."

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36. Calder, R. M., Steen, C., and Baker, L.: Blood Studies in Brucellosis, J.A.M.A. *112:* 1893, 1939.

Careful studies of the blood counts were made in several hundred cases. The leukocytes were normal, diminished, or increased. Active lymphocytosis was the most striking feature encountered.

37. Jones, D., Metzger, H. J., Schatz, A., and Waksman, S. A.: Control of Gram-negative Bacteria in Experimental Animals by Streptomycin, Science *100:* 103, 1944.

It was inevitable that streptomycin, an antibiotic potent against gram-negative bacteria would be tried against Brucella. Waksman, the discoverer of this antibiotic, himself here reports the protection of 15-day chick embryos against infection with Brucella by treatment with streptomycin, when untreated controls succumbed. A little later, I. Live, F. G. Sperling, and E. L. Stubbs (Effect of Streptomycin on Experimental Brucellosis in Guinea Pigs, Am. J. M. Sc. *211:* 267, 1946) found that 2,000 units of streptomycin daily in six doses seemed to eliminate the infection from most guinea pigs when treatment was begun one week after infection.

W. H. Hall and W. W. Spink (Therapy of Experimental Brucella Infection in the Developing Chick Embryo. I. Infection and Therapy via the Allantoic Sac, J. Immunol. *59:* 379, 1948) later developed a method to test therapeutic agents against Brucella by injection into the allantoic sac of the developing chick embryo. Sulfadiazine and streptomycin in combination were found to be more effective against *Br. abortus* and *Br. suis* than either drug alone. J. M. Shaffer and W. W. Spink (III. The Synergistic Action of Streptomycin and Sulfadiazine, ibid. *60:* 405, 1948) with the same technique soon showed that such combined

action represented a true synergism. R. Magoffin, D. Anderson, and W. W. Spink (IV. Therapy With Aureomycin, ibid. *62:* 125, 1949) explored Aureomycin alone and in combination with other agents.

38. Reimann, H. O., Price, A. H., and Elias, W. F.: Streptomycin for Certain Systemic Infections and Its Effect on the Urinary and Fecal Flora, Arch. Int. Med. *76:* 269, 1945.

In contrast to its apparent effect in experimental brucellosis (Ref. 37) streptomycin has been reported of doubtful value in human infection. Thus Reimann states that treatment with streptomycin was inconclusive in three cases. D. E. Nichols and W. E. Herrell (Streptomycin, Its Clinical Use and Limitations, J.A.M.A. *132:* 200, 1946) also found the results of treatment of brucellosis disappointing in a number of cases, although in some it had a temporary suppressive effect. However, W. H. Hall and W. W. Spink (In Vitro Sensitivity of Brucella to Streptomycin: Development of Resistance During Streptomycin Treatment, Proc. Soc. Exper. Biol. & Med. *64:* 403, 1947) found most strains of Brucella sensitive to streptomycin in the test tube although one strain from a patient with Brucella endocarditis became resistant during therapy, and G. H. Finch (Streptomycin Therapy in Undulant Fever, Am. J. Med. *2:* 485, 1947) thought he obtained favorable results in several cases.

39. Pulaski, E. J., and Amspacher, W. H.: Streptomycin Therapy for Certain Infections of Intestional Origin. New England J. Med. *237:* 419, 1947.

The authors treated two acute cases of brucellosis with a combination of streptomycin and sulfonamide therapy, which seemed to produce a cure. C. W. Eisele and N. B. McCullough independently tried the same device; the simultaneous use of streptomycin and sulfadiazine seemed to produce a cure when either drug used separately failed. "A prolonged constant septicemia promptly ceased" and no relapse occurred in a seventeen-month period. W. W. Spink, W. H. Hall, J. M. Schaffer, and A. I. Braude (Human Brucellosis, Its Specific Treatment With a Combination of Streptomycin and Sulfadiazine, J.A.M.A. *136:* 382, 1948), following successful trials in chick embryos (Ref. 37), treated nine patients with a combination of sulfadiazine and streptomycin with "more satisfactory results than any other therapy used to date." They advise streptomycin intramuscularly in doses of 0.5 Gm. every six hours for seven days and sulfadiazine with an initial oral dose of 4 Gm. and then 1 Gm. every four hours for at least two weeks. These writers later amplified their results (Treatment of Brucellosis With Streptomycin and a Sulfonamide Drug, ibid. *139:* 352, 1949). Although not absolutely secure, this form of therapy is followed by fewer relapses, and the appearance of streptomycin-resistant Brucella has not occurred.

40. Spink, W. W., Braude, A. I., Castenada, M. R., and Goytra, R. S.: Aureomycin Therapy in Human Brucellosis due to Brucella Melitensis, J.A.M.A. *138:* 1145, 1948.

Working in Mexico with patients ill with undulant fever due to *Br. melitensis* in contrast to those seen in Iowa with disease due to *Br. abortus*, the writers found Aureomycin by mouth the most effective remedy. However, they have some

reservations and in an addendum at the end of the paper there is some tempering of enthusiasm because of relapses. Enthusiastic reports also soon appeared from various sources such as those of M. S. Boyer, E. B. Schoenbach, R. M. Wood, and P. H. Long (The Treatment of Acute Brucellosis With Aureomycin, Bull. Johns Hopkins Hosp. *84:* 444, 1949) and of V. Knight, F. Ruiz-Sanchez, A. Ruiz-Sanchez, and W. McDermott (Aureomycin in Typhus and Brucellosis, Am. J. Med. *6:* 407, 1949). Later W. W. Spink, W. H. Hall, and R. Magoffin (Follow-up Study of Therapy in Forty-eight Culturally Proved Cases of Brucellosis: Streptomycin and Sulfadiazine, Aureomycin, and Chloramphenicol [Chloromycetin(R)], Arch. Int. Med. *88:* 419, 1951) reported follow-up studies of 48 patients treated with various combinations of antibiotics and sulfonamides. The results with streptomycin and sulfadiazine, and with Aureomycin seemed about equal, about one-half recovering promptly and remaining well; with chloramphenicol the results were not quite so good. So too in an elaborate study, E. M. Yow and W. W. Spink (Experimental Studies on the Action of Streptomycin, Aureomycin and Chloromycetin on Brucella, J. Clin. Invest. *28:* 871, 1949) found strains of *Br. abortus*, *Br. suis*, and *Br. melitensis* all sensitive in vitro to the three antibiotics. The action of streptomycin was bactericidal, while Aureomycin and Chloromycetin were bacteriostatic. A little later, W. E. Herrell and T. E. Barber (A New Method for Treatment of Brucellosis, J.A.M.A. *144:* 519, 1950) reported good results from treatment with a combination of Aureomycin by mouth and streptomycin intramuscularly.

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41. Knight, V., Sanchez, F. R., and Sanchez, A. R.: Terramycin in the Treatment of Human Brucellosis, Arch. Int. Med. *87:* 835, 1951.

In the hope of finding an antibiotic therapy for brucellosis which would not be followed by relapses, the authors used Terramycin, which proved highly effective in the treatment of the acute manifestations. There were, however, a significant number of relapses.

42. Abernethy, Robert, and Spink, Wesley W.: The Influence of Cortisone and Adrenocorticotrophic Hormone on Brucellosis. I. Cortisone in Experimentally Infected Animals, J. Clin. Invest. *31:* 945, 1952.

In mice with acute brucellosis, steroids converted a relatively mild infection into a fulminating and fatal illness. In contrast, cortisone did not appear to alter the course of the disease nor the tissue reactions in chronically infected animals. In contrast also, ACTH administered to a patient with acute brucellosis (W. W. Spink and W. H. Hall: II. Adrenocorticotrophic Hormone (ACTH) in Acute and Chronic Human Brucellosis, ibid., p. 958) was accompanied by prompt and remarkable improvement although the blood cultures remained positive. "The only indication for cortisone or ACTH at the present time in acute or chronic brucellosis is in patients who are quite ill and toxic. And even then, treatment should be carried out only for a few days and simultaneously with antibiotic therapy."

43. Spink, W. W.: Some Biological and Clinical Problems Related to Intracellular Parasitism in Brucellosis, New England J. Med. *247:* 603, 1952.

In an important paper Spink puts his finger on the difficulty involved in all chemotherapy and antibiotic therapy of brucellosis, the intracellular situation of the parasite which guards it against the action of chemicals, antibiotics, and sera which may be lethal in the test tube. He reviews and analyzes the whole subject with comprehensive bibliography. In another paper (Shaffer, J. M., Kucera, C. J., and Spink, W. W.: The Protection of Intracellular Brucella Against Therapeutic Agents and the Bactericidal Action of Serum, J. Exper. Med. *97:* 77, 1953) Spink and his associates devised a method for the study of intracellular Brucella in vitro. Such Brucella were protected to a great extent against the action of antibiotics. Actually no method of therapy so far devised has completely overcome this barrier; it is apparently bacteria protected against attack within cells which cause the frequent relapses in spite of therapy.

44. Spink, W. W., McCullough, N. B., Hutchings, L. M., and Mingle, C. K.: Diagnostic Criteria for Human Brucellosis, J.A.M.A. *149:* 805, 1952.

This paper is a critical appraisal by experts of the various diagnostic tests which have been used. They point out that the only unimpeachable proof of brucellosis is isolation of the organism. Agglutination in a titer of 1:320 or over allows a presumptive diagnosis. The skin test gives insecure results.

Editorials

FUND RAISING FOR MEDICAL PURPOSES: SPECIFIC DISEASES VERSUS MEDICAL EDUCATION

In *The Sun* (Baltimore), one of this country's leading newspapers, there appeared on Nov. 12, 1955, the following letter to The Editor*:

"TO THE EDITOR OF THE SUN—Sir: A recent editorial in the New England *Journal of Medicine* points out that last year the 100,000 victims of poliomyelitis in this country benefited to the extent of approximately $50,000,000 through the March of Dimes campaign, and that this amounted to a contribution of about 30 cents from every man, women and child in the United States.

"Without detracting one iota from the magnificent services performed by the National Foundation for Infantile Paralysis it is shown that a number of other causes are worthy of at least equal support.

"There are in the nation 200,000 victims of muscular dystrophy, 250,000 with multiple sclerosis, 400,000 with tuberculosis, 600,000 with cerebral palsy, 700,000 with cancer, 2,500,000 with mental disease (under treatment alone), 11,000,000 with arthritis and rheumatism, and well over 16,000,000 with heart disease (which alone causes 800,000 deaths each year). No fund campaign for the benefit of any of these groups has succeeded in collecting half as much as the March of Dimes.

"On a purely arithmetical basis it seems that if one gave 30 cents to poliomyelitis one should have given 60 cents to muscular dystrophy, 75 cents to multiple sclerosis, $1.20 for tuberculosis control, $1.80 to cerebral palsy, $2.10 to cancer, $7.50 to mental disease, $33 to arthritis and rheumatism and $49 to heart disease.

"Actually, the mythical average citizen gave only 8 cents to the campaign against heart disease, 14 cents toward cancer education, 15 cents for Christmas seals (tuberculosis) and about 1¼ cents to multiple sclerosis. Other campaigns fared no better.

"During the period extending from November 10 through December 10 the Maryland Chapter of the Arthritis and Rheumatism Foundation will conduct its fifth annual campaign for funds, for the comparatively small sum of $75,000. Within this same period of time campaigns will be held for the Muscular Dystrophy Fund ($100,000), the Maryland Society for Mentally Retarded Children ($64,000), the Maryland School for the Blind ($20,000), and the Maryland Tuberculosis Association (no goal).

**The Sun*, Baltimore, Maryland, 237, # 154, p. 10, Nov. 12, 1955. The letter to the Editor and the editorial itself are here reproduced by permission of Mr. Philip M. Wagner, Editor of the *Sun*, and Mr. Burton M. Parks, author of the letter.

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"Each of these causes is worthy of public support and each campaign has been approved by the Mayor's Co-ordinating Council For Fund Raising Campaigns. However, it is a safe assumption that four out of five of these campaigns will fail to raise the sums required to carry through next year the minimum programs they have established, and it is an equally safe assumption that all donors will complain about the number of appeals.

"The Maryland Chapter of the Arthritis and Rheumatism Foundation is most grateful for the support it has received during the last four years from the public and from the business and industry of Maryland. The chapter is convinced that by continuing to conduct separate fund campaigns the health organizations in Maryland are not only depriving themselves of adequate support, but are showing a lack of consideration to the public and the business establishments from which they seek funds.

"It is the earnest hope of the Maryland Chapter of the Arthritis and Rheumatism Foundation that before next fall the voluntary health organizations of Maryland will join together in a United Health Fund, and the chapter pledges to those who support its program this fall that the members of its board will continue their efforts of the last year to bring about a single health campaign that will result in more money for health control and research at less cost and, of equal importance, in less annoyance to those supporting these programs."

(Signed) BURTON M. PARKS,
Director, Maryland Chapter Arthritis
and Rheumatism Foundation

The Editor of *The Sun* replied to this letter in the adjoining Editorial columns, with the title and text which follows:

OPEN SEASON FOR MEDICAL APPEALS

"A correspondent, Mr. Burton M. Parks, who is director of the Maryland Chapter of the Arthritis and Rheumatism Foundation, raises a question which is as disturbing to the general public as it is to those who raise money for worthy causes. The Red Cross-Red Feather Joint Appeal drive has just been concluded. Immediately another drive begins, that of the Arthritis and Rheumatism Foundation, and will continue for a month. During that month there will also be drives for the Muscular Dystrophy Fund, the Maryland Society for Mentally Retarded Children, the Maryland School for the Blind and the Maryland Tuberculosis Association. Others will come along when these have been concluded.

"What bothers our correspondent is that this multiplicity of drives for medical ends tends to dull the responses of the giving public. When urgent pleas come thick and fast, they seem less urgent. Giving is done by caprice, and not necessarily to the most deserving cause. The success of a given drive depends more and more on the techniques of the publicity man and advertising agent. Cleverness begins to count more than worthiness. One obvious solution is to lump these medical drives together, as drives of another sort were originally lumped in the Community Fund.

"There is another weakness in these medical drives which our correspondent does not mention. It is that each of them tends to focus

the philanthropic impulse on a single disease or group of diseases rather than the whole field of medical research. Implicit in each of them is the assumption that funds for its own projects are the crying need.

"Funds for special projects are needed, beyond doubt. But ample funds for research in arthritis and rheumatism, in muscular dystrophy, problems of the mentally retarded and so forth don't go very far if in the meantime the less dramatic business of basic medical training is put on starvation rations. For specialized research, well-trained men, our medical teaching institutions and their related hospitals must be in sound shape. But who wants to give funds for the dull business of heating and lighting a hospital, keeping laboratories clean, painting the walls, installing new equipment, hiring assistants, providing adequate salaries for staff, and so on? While all these specialized funds skim off the cream of public philanthrophy and gather impressive sums to give away, basic medical education, on which every one of them leans, must skimp and scrape."

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These documents are reproduced here as an indication that an enlightened layman (the Editor of *The Sun*) is perhaps more deeply appreciative of an urgent current problem than are many physicians themselves.

The conquest of disease in general, and of most of the chronic diseases for which funds are separately sought, depends on knowledge not yet available. The acquisition of such knowledge depends on scientific research, basic and applied. The success of research in, for example, multiple sclerosis, cancer, and a host of other scourges of mankind, depends not on money alone (though this helps), nor on buildings, nor even on equipment. All the money in the world, the most beautiful of modern research buildings, the most elaborate and expensive apparatus, would be sterile and unproductive without brains to use them. It must be remembered that Einstein, who possessed one of the most brilliant scientific intellects of all time, required for space and equipment only a room, a desk, a blackboard, chalk, a pad of paper, and a pencil!

The production of brains for medical research demands good medical schools and their associated laboratories and teaching hospitals for undergraduate and graduate training. The subsequent nourishing of investigators demands opportunities for tenure (as opposed to one-year appointments on annually recurring research grants) and higher financial compensation especially in their younger years, than is presently available.

As the Editor of *The Sun* puts it, "The less dramatic business of basic medical training is put on starvation rations." Most medical school and teaching hospitals are operating at a deficit.

If these unpleasant facts are accepted as valid, then the solution of the Arthritis and Rheumatism Foundation suggested by Mr. Parks—that of a United Health Fund—needs to be carried one step further to a logical conclusion. The bulk of the monies collected by such a Fund, if established, should not be cut into the pie segments of 30 cents to poliomyelitis, $1.80 to cerebral palsy, and $49 to heart disease. Rather it should be devoted, by the Fund itself, to basic medical training and to the support of scientific investigation, basic and applied, in any field of medicine. In that happy day, if it comes, the medical scientist might be permitted to pursue his own ideas freely and independently, rather

than to be limited by subsidization—usually inadequate at that—to work often halfheartedly, and often only for the sake of a job, on a disease problem in which he may lack the spark of intense personal interest.

Those who raise funds—or contribute to them—for research in particular diseases should remember that the startling accomplishments of the past fifteen years in infectious disease control are based largely on Fleming's discovery of penicillin; that this observation was basic, not applied, and at the time apparently useless*; that it did not cost very much; and that Fleming was not sponsored by large grants from any National Foundation or Institute for the Control of Anything.

The control of chronic diseases, if accomplished, will probably depend on similar basic discoveries by investigators with trained minds, properly supported in their work. Funds are desperately needed for men, not for diseases. Given the men, diseases will be taken care of in due course.

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*Flexner Abraham: The Usefulness of Useless Knowledge, J. CHRON. DIS. 2:241, 1955.

LABORATORY TESTS FOR RHEUMATIC ACTIVITY

It is common knowledge that there is no specific diagnostic test for rheumatic fever. A series of tests (all of them nonspecific) have been employed to indicate the presence of inflammation. The purpose of these tests is to detect inflammation that could not otherwise be recognized.

The attributes of an ideal test are: (1) adequate sensitivity without a likelihood of being falsely positive, (2) sharp delineation between normal and abnormal values, (3) good correlation between extent of deviation from normal values and severity of disease activity, (4) capacity to distinguish between mere suppression of tissue reaction effected by an exogenous agent and complete resolution of inflammation, and (5) technical simplicity.

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Most of the tests in current use are related to quantitative or qualitative changes in the serum proteins that occur concurrently with the inflammatory process.

In all instances but one, the test becomes positive when a protein normally present in the blood is increased to abnormal concentration. The one exception is the C-reactive protein (CRP), which is not present in normal serum but appears soon after an inflammatory reaction or other type of tissue damage occurs, and disappears when the abnormal process subsides.

The protein fractions involved vary with the several tests. An accelerated erythrocyte sedimentation rate (ESR), for example, reflects an elevation principally in plasma fibrinogen and/or serum globulin concentration. The CRP has been characterized by Wood, McCarty, and Slater[1] as a beta globulin which is apparently combined with lipid in vivo.

Three additional tests (developed between 1948 and 1951) are all based on a rise in the mucoprotein concentration of serum or plasma. The first, reported by Winzler and his associates[2] is known simply as the serum mucoprotein test. As modified by Kelley and co-workers[3] the conjugated protein is estimated from its tyrosine content, which is measured by the intensity of the molybdenum blue color developed with Folin-Ciocalteu phenol reagent. The second, originally reported by Ayala and his co-workers[4], and modified in a report which appears in this issue of the JOURNAL OF CHRONIC DISEASES,[5] measures the mucoproteins by the intensity of a color reaction which develops when Dische's diphenylamine reagent is added to partially deproteinized serum. The third, described by Jacox,[6] estimates the serum protein by a precipitate formed when a quaternary ammonium salt is added to human serum. Whether these tests measure different, similar, or identical mucoproteins has not yet been determined.

Mucoproteins are proteins combined with polysaccharides which contain hexosamines and other hexose sugars. They are very soluble in water, not coagulated by boiling and not readily precipitated by trichloracetic or perchloric

acid. There are at least three distinct mucoproteins and they migrate, on electrophoresis in veronal buffer at pH 8.6, with alpha 1-globulins.

The most widely used tests of activity in rheumatic fever and rheumatoid rthritis are the ESR and CRP. Both have been found to be of considerable help in implementing prudent clinical management, yet both have failed to distinguish between inflammation suppressed by antirheumatic agents and true recession of the inflammatory process. Consequently, the physician has, at present, no completely dependable guide as to when therapy may be safely discontinued.

It has been reported, for instance, that when cortisone was administered to a group of children with rheumatic fever, the CRP reaction, which had been positive in all cases before treatment, became negative within a week or two after therepy. When, however, hormonal administration was discontinued, the CRP temporarily reappeared in 40 per cent of the cases and, when rheumatic activity continued, the positive reaction persisted.[7] On the other hand, Adams and his associates[8] found that the serum mucoproteins, which are also increased in rheumatic fever, return to normal levels during corticotropin therapy much more slowly than the ESR. These observers found that when corticotropin was discontinued or the dosage excessively reduced before a substantial fall in mucoprotein values had occurred, the patient had a recurrence of the disease.

Elster, Wood, and Seely[9] have reported on the relation of the CRP test done preoperatively to the presence of Aschoff bodies found in the auricular appendix removed during commissurotomy. Whereas Aschoff bodies were present in the auricular biopsies of 9 of 15 patients subjected to commissurotomy, the CRP was elevated in but 4 of these 9 patients.

Thus it is apparent that the ideal test has not yet been found. The diphenylamine (DPA) test may prove to be more sensitive than the CRP. The evidence thus far advanced on other pages of this JOPRNAL[5] is not yet conclusive, however, and it is hoped that confirmatory studies will be done in other laboratories.

In this regard two recent reports may be cited. Fearnley and co-workers[10] analyzed the sera of 23 patients with rheumatoid arthritis for DPA reaction, and correlated the results of this test with the ESR and with signs of clinical activity. They also determined the response in patients given corticotropin or steroid therapy. They found that the DPA level fell in patients receiving hormone therapy, although in some patients there were unexplained fluctuations not reflected by the ESR. They concluded that, "In patients with clinically active rheumatoid arthritis but with normal ESR, the DPA reaction was not of much value as an indication of activity"; and that in the other patients the DPA correlated with the ESR but had "no particular advantage" over it. Cecchi and Ferraris[11] did a similar study on patients with rheumatoid arthritis. These investigators found that the DPA reaction fell to normal more consistently than the ESR (in 6 of 18 patients) when steroid therapy was followed by satisfactory clinical response, and therefore concluded that the DPA test "follows the clinical variations more faithfully and more promptly than the ESR."

It is clear that further investigation and especially more critical evaluation are required before valid conclusions can be drawn as to the relative merits of the DPA reaction, the CRP test, and the ESR.

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Announcement

A series of courses in various aspects of diabetes is to be conducted in Boston under the sponsorship of the CHRONIC DISEASE PROGRAM, DIVISION OF SPECIAL HEALTH SERVICES, PUBLIC HEALTH SERVICE. The courses are to be held at the Diabetes Field Research and Training Unit, Boston, Massachusetts. Each course is one week in length. Sessions are scheduled from 9:00 A.M. to 4:00 P.M. daily.

Now in their fourth year, the courses are offered free of tuition to physicians, nurses, nutritionists, social workers, health educators, and people in related professional fields. They are designed to be of practical value to those concerned with diabetes activities.

The schedule for 1956 is as follows:

Patient Education in Diabetes, Feb. 27-March 2, 1956.
Nursing Aspects of a Diabetes Program, March 19-23, 1956.
The Clinical and Community Approach to Diabetes, April 23-27, 1956.
Nutritional Aspects of a Diabetes Program, May 21-25, 1956.
The Clinical and Community Approach to Diabetes, Oct. 1-5, 1956.

Inquiries may be addressed to U. S. Public Health Service, Diabetes Field Research and Training, 639 Huntington Avenue, Boston 15, Massachusetts.